ノクサフィル錠 100mg、同点滴静注 300mg に関する資料

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CTD 第 1 部

1.5 起原又は発見の経緯及び開発の経緯

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略号及び用語の定義

略号	定義	
C_{avg}	Average plasma concentration at steady state	平均血漿中濃度
CHMP	Committee for medicinal products for human use	欧州医薬品庁ヒト用医薬品委員会
CYP	Cytochrome P450	チトクロム P450
EU	European union	欧州連合
FDA	Food and drug administration	アメリカ食品医薬品局
GLP	Good laboratory practice	医薬品の安全性に関する非臨床試験の実施の基準
GVHD	Graft-versus-host disease	移植片対宿主病
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
HSCT	Hematopoietic stem cell transplantation	造血幹細胞移植
MK-5592、SCH56592	Posaconazole	ポサコナゾール
RH	Relative humidity	相対湿度
機構	Pharmaceuticals and medical devices agency	独立行政法人医薬品医療機器総合機構

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1.5　起原又は発見の経緯及び開発の経緯

1.5.1　起原又は発見の経緯

ポサコナゾール（SCH56592、MK-5592）は、Schering-Plough Corporation［現 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., N.J., USA (MSD)］により創製、開発された、幅広い抗真菌スペクトルを有するアゾール系抗真菌薬であり、アムホテリシン B、フルコナゾール、ボリコナゾール又はイトラコナゾールに耐性の株を含む各種酵母様真菌及び糸状菌に対して抗真菌作用を示す。

ポサコナゾールはこれまでに種々の製剤を用いて開発が進められ、その広範な非臨床試験及び臨床試験データに基づき、多くの国や地域で3種類の製剤（経口懸濁液、新錠剤及び静注用溶液）が侵襲性真菌症の予防及び治療を適応症として承認され、製造販売されている。

真菌が起こす感染症を真菌症といい、主病巣が形成される局所解剖学的部位に基づいて、表在性真菌症、深在性真菌症又は深部皮膚真菌症に大別される[資料5.4: 001]。深在性真菌症は侵襲性真菌症とも呼ばれ、血液疾患領域、呼吸器内科領域及び外科・救急・集中治療領域をはじめ、幅広い領域の患者にみられる臓器又は全身性の感染症であり、早期診断・早期治療が求められる重篤な疾患である。代表的な原因真菌に *Aspergillus* 属、*Candida* 属、*Cryptococcus* 属及びムーコル目などがある。また、本邦での頻度は少ないものの、*Fusarium* 属及び *Coccidioides* 属による感染症も知られている[資料5.4: 002]。深在性真菌症を引き起こすリスク因子としては、好中球減少、同種造血幹細胞移植（HSCT）、ステロイド投与、免疫抑制薬投与、中心静脈カテーテル留置、カンジダの定着、広域抗菌薬投与、陳旧性肺結核や間質性肺炎等の肺構造の器質的変化、HIV 感染、高齢など多数がある[資料5.4: 002]。

深在性真菌症は診断が容易ではなく、発症すると予後が不良であるため、血液疾患領域では深在性真菌症の発症割合と、その後の深在性真菌症による死亡割合を減少させるために抗真菌薬が予防投与されている[資料5.4: 002]。海外の主要なガイドラインでは、急性白血病や骨髄異形成症候群の寛解導入療法、同種 HSCT では抗真菌薬の予防投与が推奨されており[資料5.4: 002]、本邦のガイドラインでも同種 HSCT 後の抗真菌薬の予防投与が推奨されている[資料5.4: 003]。

また、深在性真菌症を発症すると急速に進行して重篤化し、抗真菌治療薬が奏効しない例も多いことから[資料5.4: 004]、確定診断まで待たずに経験的治療（Empiric therapy）や、先制攻撃的治療（Preemptive therapy）又は推定治療（Presumptive therapy）を行うことも重要となる[資料5.4: 004] [資料5.4: 005]。

深在性真菌症の治療には一般的に抗真菌治療薬が投与される。また、抗真菌治療薬が奏効しない一部の深在性真菌症の病型に対しては、病巣切除やデブリードマンなどの外科的療法が併用されることがある[資料5.4: 006]。しかし、増加傾向が注目されているムーコル症や、発症頻度は低いものの注意が必要な真菌感染症であるフサリウム症、コクシジオイデス症、クロモブラストミコーシス及び菌腫では治療の選択肢が限られている。

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現在本邦で市販されている抗真菌治療薬のうち、アムホテリシンB製剤は最も幅広い抗真菌スペクトルを有するが、副作用が強いため十分な量を投与できないことが多い。フルコナゾールに代表されるアゾール系抗真菌薬は、アムホテリシンB製剤と比較して安全性は高いものの、抗真菌スペクトルや薬物動態の面から十分な有効性があるものは少ない。ボリコナゾールは、幅広い抗菌活性を有しているものの、羞明、霧視、視覚障害などの副作用が比較的高頻度に認められ[資料5.4: 006]、ボリコナゾール投与中のブレイクスルー感染症としてムーコル症が認められることもあり[資料5.4: 007][資料5.4: 008]、使用には注意が必要である。致死性の高いムーコル症に有効な薬剤は、現状ではアムホテリシンB製剤のみである。これらのことから、既存の抗真菌治療薬では医療現場のニーズに対して十分とは言えず、広範な抗真菌活性を有し、安全性の高い薬剤の開発が期待されている。

1.5.2　品質・安定性試験の経緯

ノクサフィル®錠及びノクサフィル®点滴静注は、有効成分としてポサコナゾールをそれぞれ100 mg含有するフィルムコーティング錠及び300 mg含有する注射用濃縮液剤である。

原薬であるポサコナゾールの安定性試験として、長期保存試験（25°C/60%RH）36ヵ月間及び加速試験（40°C/75%RH）6ヵ月間の結果が得られている。これまでに得られた結果を踏まえ、本品のリテスト期間を[redacted]ヵ月と設定した[2.3.S.7項]。

ノクサフィル®錠については、長期保存試験（25°C/60%RH）36ヵ月間及び加速試験（40°C/75%RH）6ヵ月間の結果が得られている。これまでに得られた結果を踏まえ、本剤の有効期間を24ヵ月と設定した[2.3.P.8項-ポサコナゾール　錠剤]。

ノクサフィル®点滴静注については、長期保存試験（5°C/成り行きRH）36ヵ月間及び加速試験（30°C/65%RH）6ヵ月間の結果が得られている。これまでに得られた結果を踏まえ、本剤の有効期間を2～8°Cで36ヵ月と設定した[2.3.P.8項-ポサコナゾール　注射剤]。

1.5.3　非臨床試験の経緯

<u>薬効薬理及び副次的薬理・安全性薬理試験</u>

本邦で旧カプセル又は経口懸濁液を用いた第I相試験を開始するまでに、一連の *in vitro* での効力を裏付ける試験を実施し、ポサコナゾールの抗真菌作用の特徴、他剤との位置づけ、作用機序等を検討した。また、各種感染動物モデルを用いて、ポサコナゾールの用法・用量等を検討した。

今回製造販売承認申請を行う新製剤を用いた国内第Ⅲ相試験の開始とともに、国内での最新の臨床分離株の各種抗真菌薬に対する感受性を調査し、併せて海外の臨床分離株の感受性と比較するために、20[redacted]～20[redacted]年に希少真菌を含む各種臨床分離株を収集した。なお、収集が困難であった一部の希少真菌については[redacted]から菌株の分与を受けた。さらに、安全性薬理試験（一般薬理試験）については、中枢神経系、心血管系、胃腸管系及び腎機能に及ぼす影響を19[redacted]年に検討した。2001年6月21日に安全性薬理試験ガイドライン（医薬審発第902号）が通知された後に、心血管系試験として、*in vitro* でのイオンチャネル及び活動電位持続時間に及

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ぼす影響を検討した。また、*in vivo* での心血管系及び呼吸系に及ぼす影響を、医薬品の安全性に関する非臨床試験の実施の基準（GLP）に準拠して評価した。

薬物動態試験

マウス、ラット、ウサギ、イヌ及びサルにポサコナゾールを各種静注用製剤（懸濁液又は溶液）並びに経口用製剤（懸濁液、カプセル、錠剤又は混餌投与）で静脈内投与又は経口投与した際の薬物動態、組織分布、代謝及び排泄試験を実施した。また、*in vitro* 試験により、ヒト及び各動物種のポサコナゾールの血漿蛋白結合及び代謝試験を実施した。また、ポサコナゾールのチトクローム P450（CYP）、ウリジン5’-二リン酸-グルクロン酸転移酵素、P-糖蛋白質及び有機アニオン輸送ポリペプチド1B1又は1B3を介した薬物相互作用の可能性を評価した。

毒性試験

本邦での第Ⅰ相臨床試験（旧カプセルを用いた JPC-[redacted]-361-11試験）の開始までに、主要な毒性試験として、原薬を用いたマウス、ラット及びイヌの単回経口あるいは静脈内投与毒性試験、ラット及びイヌの反復（最長6ヵ月間）経口投与毒性試験、遺伝毒性試験（細菌を用いる復帰突然変異試験、ほ乳類細胞を用いる突然変異試験及び染色体異常試験、並びにマウス小核試験）、生殖発生毒性試験（ラット及びウサギの胚・胎児発生に関する試験）、並びに毒性発現の機序に関する一部試験を実施した。

本邦での第Ⅲ相臨床試験（市販予定の新錠剤及び静注用溶液を用いた P101試験）の開始までに、主要な毒性試験として、原薬を用いたイヌの12ヵ月間反復経口投与毒性試験、マウス及びラットのがん原性試験、生殖発生毒性試験（ラットの受胎能及び着床までの初期胚発生に関する試験、ラットの出生前及び出生後の発生並びに母体の機能に関する試験、幼若ラット及びイヌを用いた試験）、免疫毒性に関する試験、並びに各種毒性発現の機序に関する試験、静注用懸濁液を用いたマウス、ラット及びサルの単回静脈内投与（急性）毒性試験、ラット及びサルの反復（最長3ヵ月間）静脈内投与毒性試験、遺伝毒性試験（細菌を用いる復帰突然変異試験、ほ乳類細胞を用いる染色体異常試験、及びマウス小核試験）、局所刺激性試験並びに免疫毒性に関する試験、静注用溶液を用いたサルの1ヵ月間反復静脈内投与毒性試験及び局所刺激性試験を実施した。

これらの毒性試験成績については、20[redacted]年[redacted]月[redacted]日の独立行政法人医薬品医療機器総合機構（機構）との医薬品[redacted]相談[redacted]において、[redacted]との助言を受領した。その後、追加で静注用溶液を用いた幼若及び成熟イヌの反復（最長3ヵ月間）静脈内投与毒性試験を実施した。重要な毒性試験はいずれも、GLP に準拠して実施した。

1.5.4　臨床試験の経緯

1.5.4.1　海外臨床試験の概要

臨床薬理試験

海外の各種臨床薬理試験では、忍容性及び安全性を評価するとともに、以下に示す薬物動態の

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検討を行った。また、一部の試験では心電図パラメータも評価した。

健康被験者を対象に、単回及び反復経口及び静脈内投与時の血漿中薬物動態評価に加え、皮膚中（P05270試験）、及び肺上皮被覆液中並びに肺胞上皮細胞内（P04547試験）の薬物動態、マスバランス（C[redacted]-104試験及びP02418試験）を評価した。また、年齢及び性別（P02810試験）、人種（P02811試験）、肝機能障害（[redacted]-195試験及びP03742試験）及び腎機能障害（P01940試験）の影響を評価する薬物動態試験を実施した。併用薬との薬物相互作用については、薬物代謝酵素誘導剤やCYP3A4の基質となる薬剤を含む種々の薬剤で検討した。

ポサコナゾールの市販予定製剤（新錠剤及び／又は静注用溶液）を用いて、新錠剤（市販予定製剤）の絶対的バイオアベイラビリティ（P07783試験）、新錠剤（市販予定製剤）での食事の影響（P112試験）を検討した。

また、侵襲性真菌症を発症するリスクの高い被験者でのポサコナゾールの薬物動態を検討した［P05615試験及びP117試験（新錠剤）、並びにP05520試験（静注用溶液及び経口懸濁液）］。なお、これらの試験のうちP05615試験及びP05520試験は後期第Ⅰ相／第Ⅲ相試験であり、後期第Ⅰ相パート後に、第Ⅲ相パートを実施した。

<u>第Ⅱ相試験及び第Ⅲ相試験</u>

患者を対象としたポサコナゾール経口懸濁液の開発は、口腔咽頭カンジダ症患者を対象とした治療試験で開始し、引き続き、重篤疾患であり医療上の必要性が高いと考えられた侵襲性真菌症患者を対象に有効性、安全性及び薬物動態を評価した。

侵襲性真菌症患者を対象とした海外第Ⅱ相臨床試験では、ポサコナゾール旧カプセル（C/I97-280試験）はコクシジオイデス症に対して有効で、忍容性も良好であった。また、免疫不全の難治性侵襲性真菌症又は抗真菌薬の経験的治療が必要な発熱性好中球減少症患者を対象とした海外第Ⅱ相用量比較試験（P01893試験）では、ポサコナゾール経口懸濁液は難治性侵襲性真菌症及び発熱性好中球減少症に対して有効性を示し、用量に依存した有害事象は認められなかった。

侵襲性真菌症患者を対象とした臨床試験としては、標準抗真菌薬が無効又は不耐容の患者を対象に第Ⅲ相試験を非盲検、非対照試験として実施した（P00041試験）。また、P00041試験の実施とほぼ同時期に同一医療機関において、P00041試験の選択・除外基準とほぼ同様の条件を満たす患者に対して実施された救済治療としての標準的抗真菌治療の有効性データについてレトロスペクティブに調査するP02387試験を実施した。ポサコナゾール群（P00041試験）及び外部対照群（P02387試験）の侵襲性真菌症診断を含む患者の試験組入れの適格性及び有効性を外部の独立効果判定委員会評価者が盲検下で判定し、それらを併せてP02952試験として結果をまとめることで、*Aspergillus* 属、*Fusarium* 属、*Coccidioides* 属、ムーコル目、クロモブラストミコーシス及び菌腫の原因真菌、*Candida* 属及び *Cryptococcus* 属による侵襲性真菌症でのポサコナゾールの有効性及び安全性の評価を行った。

侵襲性真菌症のハイリスク患者［同種HSCT後の移植片対宿主病（GVHD）患者］を対象とした海外第Ⅲ相試験（C/I98-316試験）では、侵襲性真菌症の予防効果において、ポサコナゾール経口懸濁液は、対照薬であるフルコナゾールに対する非劣性を示した。また、ポサコナゾール経口

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懸濁液とフルコナゾールに認められた安全性プロファイルは同様で、忍容性は良好であった。さらに、侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症が確認又は予測される患者）を対象とした海外第Ⅲ相試験（P01899試験）では、侵襲性真菌症の予防効果において、ポサコナゾール経口懸濁液は、対照薬である標準的アゾール系抗真菌薬（フルコナゾール又はイトラコナゾール）に対する優越性を示した。ポサコナゾール経口懸濁液とフルコナゾール又はイトラコナゾールに認められた安全性プロファイルは類似しており、忍容性は良好であった。

臨床的に適切な治療がすべて無効であった侵襲性真菌症患者又はポサコナゾールを用いた維持療法の継続若しくは二次予防が必要な侵襲性真菌症患者を対象に安全性を評価した海外後期第Ⅲ相試験（P02095試験）では、ポサコナゾール経口懸濁液の投与は概して安全で、良好な忍容性が認められた。

また、経口懸濁液を用いた主要な第Ⅲ相試験（C/I98-316試験、P00041試験及び P01899試験）の結果に基づき、米国規制当局（FDA）及び EU 規制当局（CHMP）との相談のもとポサコナゾールの有効性の目標曝露量（定常状態での C_{avg} が90%以上の被験者で500 ng/mL 以上となること）が設定された。海外における新錠剤及び静注用溶液の開発は、この目標曝露量を達成できるように進めた[2.7.2.1.4.1項]。侵襲性真菌症のハイリスク患者（血液悪性腫瘍疾患に対する化学療法に伴う好中球減少症が確認又は予測される患者並びに同種 HSCT 後の GVHD の治療又は予防患者）を対象としたポサコナゾール新錠剤予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05615試験）並びにポサコナゾール静注用溶液及び経口懸濁液予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05520試験）の2試験の第Ⅰ相パートでは、臨床推奨用量（いずれの製剤でも、ポサコナゾール1回300 mg を初日は1日2回、2日目以降は1日1回投与）での新錠剤及び静注用溶液の投与により目標曝露量に達することが確認された。また、第Ⅲ相パートでは、新錠剤及び静注用溶液の投与による侵襲性真菌症の発症率は低く、経口懸濁液と類似した有効性が認められ、ポサコナゾール新錠剤及び静注用溶液の安全性プロファイルは経口懸濁液と類似しており、忍容性も良好であった。

なお、ポサコナゾール経口懸濁液では、口腔咽頭カンジダ症患者の一次治療及びアゾール耐性の口腔咽頭カンジダ症患者を対象とした臨床試験において、ポサコナゾールの口腔咽頭カンジダ症に対する有効性が認められている。

1.5.4.2　　国内臨床試験の概要

臨床薬理試験

本邦では、19[redacted]年から20[redacted]年に日本人健康被験者を対象として、旧カプセルで1試験（JPC-[redacted]-361-11試験）及び経口懸濁液で3試験（JPC-[redacted]-361-12試験、I-P05011試験及び I-P05014試験）の計4つの第Ⅰ相試験を実施した。しかし、旧カプセルでは製剤サイズが大きく、被験者の服用が困難になることが予想され、経口懸濁液では吸収性の改善等を要すると考えられたため、これらの製剤での国内開発を進めなかった。その後、海外で食事条件にかかわらず十分な血中濃度を達成できると考えられる新製剤（新錠剤及び静注用溶液）の開発に目処が立ったことから、本邦でもこれらの製剤で開発を進めることとし、国内第Ⅲ相試験に先立ち、20[redacted]年に日本人健康

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男性を対象とした新錠剤及び静注用溶液の市販予定製剤を用いた第Ⅰ相試験（P067試験）を実施した。その結果、ポサコナゾール200～600 mg の単回経口投与、ポサコナゾール300 mg の単回末梢静脈内投与、及びポサコナゾール200及び400 mg の1日1回（1日目のみ1日2回）10日間反復経口投与時の忍容性は概して良好であった。また、日本人健康被験者にポサコナゾール300 mg 単回末梢静脈内投与及びポサコナゾール200及び400 mg 1日1回（1日目のみ1日2回）10日間反復経口投与した際の薬物動態は非日本人健康被験者（P05637試験及び P06356試験）と類似していた。

第Ⅲ相試験

本邦では、深在性真菌症（侵襲性アスペルギルス症、慢性肺アスペルギルス症、フサリウム症及びムーコル症）の日本人患者を対象としたポサコナゾール新錠剤及び静注用溶液の安全性、有効性及び薬物動態を検討する実薬対照、非盲検第Ⅲ相試験（P101試験）を、機構相談（[redacted]：[redacted]）に基づいて計画した。試験は海外での臨床推奨用量（いずれの製剤でも、ポサコナゾール1回300 mg を初日は1日2回、2日目以降は1日1回投与）と同じ用法・用量を用いて開始されたが、ポサコナゾール群で早期中止率が高い傾向がみられたため、患者登録を一時中断した。予備的な薬物動態解析の結果、非日本人患者と比べて、ポサコナゾールの血漿中濃度が高いことが観察され、高曝露量の要因として低体重の影響が示唆された。これらの解析結果及び医薬品[redacted]相談（[redacted]）により得られた機構の助言も踏まえ、45 kg 未満の被験者を除外する治験実施計画書の改訂を行い、中断前の集団をコホート1、治験実施計画書改訂後の集団をコホート2として P101試験を再開した。フサリウム症患者の組入れはなかったが、それ以外は当初計画した目標評価症例数の被験者を組み入れ、試験は終了した。

その結果、P101試験に参加した日本人の深在性真菌症患者で、海外での新錠剤及び静注用溶液の開発時に設定したポサコナゾールの有効性の目標曝露量を達成した。また、ムーコル症の治療において、良好な治療効果を示した。

また、輸入真菌症であるコクシジオイデス症は海外分離株の感受性データしかないが、フサリウム症、クロモブラストミコーシス及び菌腫の原因真菌のポサコナゾールに対する感受性に国内外で差が認められず[2.7.3.3.2.1.1 項]、発現頻度が低いこれらの真菌症に関して海外有効性データを使用する際の条件をいずれも満たしており[2.7.3.3.2.1 項]、非日本人の真菌症患者で認められたポサコナゾールの治療効果と同様の効果が日本人の真菌症患者でも認められると考えられた。

また、上記の原因真菌に加えて、深在性真菌症のハイリスク患者での分離頻度が最も高い、*Aspergillus* 属、*Candida* 属の臨床分離株の感受性についても、国内外で明らかな差がないことが確認されている。

また、日本人の深在性真菌症のハイリスク患者での予防試験は実施していないが、母集団薬物動態モデルに基づくシミュレーション結果より、日本人の深在性真菌症のハイリスク患者でのポサコナゾールの曝露量（C_{avg}）は非日本人のハイリスク患者と類似した分布を示すと予測され、日本人のハイリスク患者でも非日本人のハイリスク患者と同様の予防効果を示すと考えられた。

これら、国内外のエビデンスから、以下の効能又は効果並びに用法及び用量にて製造販売承認

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申請を行うこととした。

効能又は効果

- 造血幹細胞移植患者又は好中球減少が予測される血液悪性腫瘍患者における深在性真菌症の予防
- 下記の真菌症の治療

フサリウム症、ムーコル症、コクシジオイデス症、クロモブラストミコーシス及び菌腫

用法及び用量

- 新錠剤

通常、成人にはポサコナゾールとして初日は1回300 mg を1日2回、2日目以降は300 mg を1日1回経口投与する。

- 静注用溶液

通常、成人にはポサコナゾールとして初日は1回300 mg を1日2回、2日目以降は300 mg を1日1回、中心静脈ラインから約90分間かけて緩徐に点滴静注する。

1.5.5　開発の経緯

ポサコナゾールに関する開発の経緯図を[図 1.5-1]、[図 1.5-2]及び[図 1.5-3]に示す。

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図 1.5-1　ポサコナゾールの開発の経緯図[redacted]

試験項目		
非臨床試験	薬理試験	薬効薬理試験 副次的薬理・安全性薬理試験
	薬物動態	吸収・分布・代謝・排泄
	毒性試験	単回投与毒性 反復投与毒性 遺伝毒性 がん原性 生殖発生毒性 局所刺激性 その他
第Ⅰ相試験		臨床薬理試験［参考資料］
第Ⅱ相試験		経口懸濁液治療の用量比較試験（P01893 試験）［参考資料］†
		コクシジオイデス症患者試験（C/I97-280 試験）［参考資料］‡
第Ⅲ相試験		経口懸濁液予防投与試験（P01899 試験）［評価資料］§
		経口懸濁液予防投与試験（C/I98-316 試験）［評価資料］‖
		P00041 試験と P02387 試験の有効性結果の比較（P02952 試験）［評価資料］¶ 経口懸濁液治療試験（P00041 試験）［評価資料］# 標準治療レトロスペクティブ試験（P02387 試験）［評価資料］††
		限定アクセス治療試験（P02095 試験）［参考資料］‡‡

図中の4桁の数字は年を、1～2桁の数字は月を示す。---------：海外で実施
† 難治性侵襲性真菌症患者又は発熱性好中球減少症患者を対象としたポサコナゾール経口懸濁液治療の海外第Ⅱ相 用量比較試験（P01893試験）［参考資料］
‡ コクシジオイデス症患者を対象としたポサコナゾール旧カプセルの海外第Ⅱ相試験（C/I97-280試験）［参考資料］
§ 侵襲性真菌症ハイリスク患者（好中球減少症患者）を対象としたポサコナゾール経口懸濁液予防投与の海外第Ⅲ相試験（P01899試験）［評価資料］
‖ 侵襲性真菌症ハイリスク患者（造血幹細胞移植患者）を対象としたポサコナゾール経口懸濁液予防投与の海外第Ⅲ相試験（C/I98-316試験）［評価資料］
¶ 侵襲性真菌症患者を対象とした海外第Ⅲ相試験（P00041試験と P02387試験）の有効性結果の比較（P02952試験）［評価資料］
# 侵襲性真菌症患者を対象としたポサコナゾール経口懸濁液治療の海外第Ⅲ相試験（P00041試験）［評価資料］
†† 侵襲性真菌症患者を対象とした標準的抗真菌薬治療の有効性を調査する海外レトロスペクティブ試験（P02387試験）［評価資料］
‡‡ 侵襲性真菌症患者を対象としたポサコナゾール経口懸濁液の海外後期第Ⅲ相限定アクセス治療試験（P02095試験）［参考資料］

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図 1.5-2　ポサコナゾールの開発の経緯図[redacted]

試験項目		
非臨床試験	薬理試験	薬効薬理試験 副次的薬理・安全性薬理試験
	薬物動態	吸収・分布・代謝・排泄
	毒性試験	単回投与毒性 反復投与毒性 遺伝毒性 がん原性 生殖発生毒性 局所刺激性 その他
第Ⅰ相試験		臨床薬理試験［参考資料］
後期第Ⅰ相／第Ⅲ相試験		新錠剤予防投与試験 （P05615 試験）［評価資料］†
		静注用溶液及び経口懸濁液予防投与試験 （P05520 試験）［評価資料］‡
第Ⅲ相試験		経口懸濁液予防投与試験 （P01899 試験）［評価資料］§
		経口懸濁液予防投与試験 （C/I98-316 試験）［評価資料］‖
		P00041 試験と P02387 試験の有効性結果の比較 （P02952 試験）［評価資料］¶
		限定アクセス治療試験 （P02095 試験）［参考資料］#

[redacted]

図中の4桁の数字は年を、1～2桁の数字は月を示す。---------：海外で実施
† 侵襲性真菌症ハイリスク患者（好中球減少症患者／同種造血幹細胞移植患者）を対象としたポサコナゾール新錠剤予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05615試験）［評価資料］
‡ 侵襲性真菌症ハイリスク患者（好中球減少症患者／同種造血幹細胞移植患者）を対象としたポサコナゾール静注用溶液及び経口懸濁液予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05520試験）［評価資料］
§ 侵襲性真菌症ハイリスク患者（好中球減少症患者）を対象としたポサコナゾール経口懸濁液予防投与の海外第Ⅲ相試験（P01899試験）［評価資料］
‖ 侵襲性真菌症ハイリスク患者（造血幹細胞移植患者）を対象としたポサコナゾール経口懸濁液予防投与の海外第Ⅲ相試験（C/I98-316試験）［評価資料］
¶ 侵襲性真菌症患者を対象とした海外第Ⅲ相試験（P00041試験と P02387試験）の有効性結果の比較（P02952試験）［評価資料］
# 侵襲性真菌症患者を対象としたポサコナゾール経口懸濁液の海外後期第Ⅲ相限定アクセス治療試験（P02095試験）［参考資料］

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図 1.5-3　ポサコナゾールの開発の経緯図[redacted]

試験項目			
安定性試験		原薬	長期保存試験
			加速試験
		製剤（錠剤）	長期保存試験
			加速試験
		製剤（注射剤）	長期保存試験
			加速試験
非臨床試験	薬理試験	薬効薬理試験 副次的薬理・安全性薬理試験	
	薬物動態	吸収・分布・代謝・排泄	
	毒性試験	単回投与毒性 反復投与毒性 遺伝毒性 がん原性 生殖発生毒性 局所刺激性 その他	
第Ⅰ相試験		臨床薬理試験［参考資料］	
		日本人：新錠剤及び静注用溶液 第Ⅰ相試験（P067試験）［評価資料］†	
後期第Ⅰ相試験		中国人：新錠剤 後期第Ⅰ相試験（P117 試験）［参考資料］‡	
後期第Ⅰ相／第Ⅲ相試験		新錠剤予防投与試験 （P05615 試験）［評価資料］§	
		静注用溶液及び経口懸濁液予防投与試験 （P05520 試験）［評価資料］‖	
第Ⅲ相試験		日本人：新錠剤及び静注用溶液治療試験（P101試験）［評価資料］¶	

図中の4桁の数字は年を、1～2桁の数字は月を示す。　　=====：本邦で実施、---------：海外で実施

† 日本人健康被験者を対象としたポサコナゾール新錠剤及び静注用溶液の単回及び反復経口投与並びに単回末梢静脈内投与試験（P067試験）［評価資料］

‡ 侵襲性真菌症ハイリスク中国人患者を対象としたポサコナゾール新錠剤反復投与の海外後期第Ⅰ相試験（P117試験）［参考資料］

§ 侵襲性真菌症ハイリスク患者（好中球減少症患者／同種造血幹細胞移植患者）を対象としたポサコナゾール新錠剤予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05615試験）［評価資料］

‖ 侵襲性真菌症ハイリスク患者（好中球減少症患者／同種造血幹細胞移植患者）を対象としたポサコナゾール静注用溶液及び経口懸濁液予防投与の海外後期第Ⅰ相／第Ⅲ相試験（P05520試験）［評価資料］

¶ 深在性真菌症患者を対象としたポサコナゾール新錠剤及び静注用溶液治療の国内第Ⅲ相試験（P101試験）［評価資料］

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CTD 第 1 部
1.6 外国における使用状況等に関する資料

MSD 株式会社

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1.6　外国における使用状況等に関する資料

1.6.1　外国における使用状況等

2018年10月現在、本薬の各製剤の米国、欧州連合（ドイツ、フランス等）及びオーストラリアを含む国又は地域での承認状況は下記のとおりである。

- 経口懸濁液
  73の国又は地域
- 新錠剤（別称：徐放錠、腸溶錠）
  51の国又は地域
- 静注用溶液（別称：静注用濃厚溶液）
  42の国又は地域

米国、欧州連合及びオーストラリアでの承認状況を[表 1.6-1]に示す。

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表 1.6-1 海外での主な承認状況

国名	販売名	承認年月	剤形・含量	用法・用量
米国	NOXAFIL	2006年9月	経口懸濁液 1 mL 中に40 mg 含有	侵襲性アスペルギルス症及びカンジダ症の予防 200 mg（5 mL）を1日3回服用 投与期間は好中球減少症又は免疫抑制からの回復に基づく 口腔咽頭カンジダ症の治療 負荷用量：初日に100 mg（2.5 mL）を1日2回服用 維持用量：2日目以降は100 mg（2.5 mL）を1日1回13日間服用 イトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症を含む口腔咽頭カンジダ症の治療 400 mg（10 mL）を1日2回服用 投与期間は患者の基礎疾患の程度及び臨床効果に基づく
		2013年11月	徐放錠 100 mg 錠	侵襲性アスペルギルス症及びカンジダ症の予防 負荷用量：初日に300 mg（100 mg 徐放錠3錠）を1日2回服用 維持用量：2日目以降は300 mg（100 mg 徐放錠3錠）を1日1回服用 投与期間は好中球減少症又は免疫抑制からの回復に基づく
		2014年3月	静注用溶液 1バイアル中に 300 mg 1 mL 中に18 mg 含有	侵襲性アスペルギルス症及びカンジダ症の予防 負荷用量：初日に300 mg を1日2回点滴静注 維持用量：2日目以降は300 mg を1日1回点滴静注 投与期間は好中球減少症又は免疫抑制からの回復に基づく
効能・効果				
移植片対宿主病を有する造血幹細胞移植患者又は化学療法により遷延した好中球減少症を伴う血液悪性腫瘍患者を含む重度の免疫不全状態で侵襲性アスペルギルス症及びカンジダ症を発症するリスクが高い患者におけるこれらの感染症の予防 ・ポサコナゾール静注用溶液は18歳以上の患者での予防を適応とする ・ポサコナゾール徐放錠及び経口懸濁液は13歳以上の患者での予防を適応とする 経口懸濁液のみ： イトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症を含む口腔咽頭カンジダ症の治療				

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表 1.6-1 海外での主な承認状況（続き）

国名	販売名	承認年月	剤形・含量	用法・用量
欧州連合	Noxafil	2005年10月	経口懸濁液 1 mL 中に40 mg 含有	難治性侵襲性真菌症／一次療法に不耐容の侵襲性真菌症の治療 200 mg（5 mL）を1日4回服用 食事や栄養補助剤を摂取可能な場合、食事中又は食後速やかに400 mg（10 mL）を1日2回服用 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づく 口腔咽頭カンジダ症の治療 初日に200 mg（5 mL）を1日1回、その後は100 mg（2.5 mL）を1日1回13日間服用 吸収のため食事（摂食困難な場合は栄養補助剤の摂取）中又は食後すぐに服用 侵襲性真菌症の予防 200 mg（5 mL）を1日3回服用 吸収のため食事（摂食困難な場合は栄養補助剤の摂取）中又は食後すぐに服用 投与期間は好中球減少症又は免疫抑制からの回復に基づく AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する
効能・効果 成人における以下の真菌感染の治療： ・アムホテリシン B 及びイトラコナゾールが無効†又は不耐容の患者における侵襲性アスペルギルス症 ・アムホテリシン B が無効又は不耐容の患者におけるフサリウム症 ・イトラコナゾールが無効又は不耐容の患者におけるクロモブラストミコーシス及び菌腫 ・アムホテリシン B、イトラコナゾール及びフルコナゾールが無効又は不耐容の患者におけるコクシジオイデス症 侵襲性真菌症の予防 ・寛解導入化学療法施行中の急性骨髄性白血病（AML）又は骨髄異形成症候群（MDS）患者で、好中球減少症が遷延することが予測され、侵襲性真菌症を発症するリスクが高い患者における侵襲性真菌症の予防 ・移植片対宿主病に対し高用量免疫抑制療法を行う造血幹細胞移植患者で、侵襲性真菌症を発症するリスクが高い患者における侵襲性真菌症の予防 経口懸濁液のみ： 口腔咽頭カンジダ症の一次療法としての治療 ・局所療法が無効†であると予測される重度の疾患又は免疫不全患者における口腔咽頭カンジダ症の一次療法としての治療 † 無効とは有効な抗真菌薬の治療用量で最短7日間投与後、感染進行したこと又は改善がみられないことと定義する		2014年4月	腸溶錠 100 mg 錠	難治性侵襲性真菌症／一次療法に不耐容の侵襲性真菌症の治療 初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用 食事に関係なく服用可能 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づく 侵襲性真菌症の予防 初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用 食事に関係なく服用可能 投与期間は好中球減少症又は免疫抑制からの回復に基づく AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する
		2014年9月	静注用濃厚溶液 1バイアル中に 300 mg 1 mL 中に18 mg 含有	難治性侵襲性真菌症／一次療法に不耐容の侵襲性真菌症の治療 初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づく 侵襲性真菌症の予防 初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与 投与期間は好中球減少症又は免疫抑制からの回復に基づく AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する

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表 1.6-1 海外での主な承認状況（続き）

国名	販売名	承認年月	剤形・含量	用法・用量
オーストラリア	NOXAFIL	2006年3月	経口懸濁液 1 mL 中に40 mg 含有	難治性侵襲性真菌症／他の治療に不耐容の侵襲性真菌症の治療 400 mg（10 mL）を1日2回、食事又は240 mL の栄養補助剤とともに服用 侵襲性真菌症の予防 200 mg（5 mL）を1日3回服用 投与期間は好中球減少症又は免疫抑制からの回復に基づく HIV 感染患者における口腔咽頭カンジダ症の治療 初日に200 mg（5 mL）を1日1回、その後は100 mg（2.5 mL）を1日1回13日間服用 HIV 感染患者におけるイトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症の治療 400 mg（10 mL）を1日2回服用
効能・効果		2014年11月	徐放錠 100 mg 徐放錠	難治性侵襲性真菌症／他の治療に不耐容の侵襲性真菌症の治療 初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用 食事に関係なく服用可能 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づく 侵襲性真菌症の予防 初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用 投与期間は好中球減少症又は免疫抑制からの回復に基づく
他の治療が不耐容又は無効な患者（経口懸濁液及び徐放錠は13歳以上、静注用濃厚溶液は成人）における以下の侵襲性真菌症の治療： ・侵襲性アスペルギルス症 ・フサリウム症 ・ムーコル症 ・コクシジオイデス症 ・クロモブラストミコーシス及び菌腫 持続性好中球減少症又は造血幹細胞移植患者のような侵襲性真菌症を発症するリスクが高い患者（経口懸濁液及び徐放錠は13歳以上、静注用濃厚溶液は成人）における侵襲性真菌症の予防 <u>経口懸濁液のみ：</u> イトラコナゾール及びフルコナゾールが無効な疾患を有する患者を含む、免疫抑制状態の成人における口腔咽頭カンジダ症の治療		2015年1月	静注用濃厚溶液 1バイアル中に 300 mg 1 mL 中に18 mg 含有	難治性侵襲性真菌症／他の治療に不耐容の侵襲性真菌症の治療 初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づく 侵襲性真菌症の予防 初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与 投与期間は好中球減少症又は免疫抑制からの回復に基づく AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する

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1.6.2　外国の添付文書

1.6.2.1　外国の添付文書の概要（和訳）

1.6.2.1.1　米国添付文書の概要（和訳）

販売名

NOXAFIL 静注用溶液
NOXAFIL 徐放錠（経口用）
NOXAFIL 経口懸濁液

剤形・含量

ポサコナゾール静注用溶液は、バイアル用シールストッパーとアルミニウムシールで閉めたType 1のガラスバイアルとして供給している。バイアル中に含まれる総量は、溶液16.7 mL に300 mg（1 mL 中にポサコナゾール18 mg）である。

ポサコナゾール100 mg 徐放錠は、コーティングされた黄色の長円形の錠剤であり、片側に「100」と刻印されている。

ポサコナゾール経口懸濁液は、チャイルドレジスタントキャップを施した褐色のガラスボトル（4オンス123 mL）として供給している。懸濁液105 mL（1 mL 中にポサコナゾール40 mg）が充填されている。

効能・効果

1)　侵襲性アスペルギルス症及びカンジダ症の予防

ポサコナゾール静注用溶液、徐放錠及び経口懸濁液は、移植片対宿主病を有する造血幹細胞移植患者又は化学療法により遷延した好中球減少症を伴う血液悪性腫瘍患者を含む重度の免疫不全状態で侵襲性アスペルギルス症及びカンジダ症を発症するリスクが高い患者におけるこれらの感染症の予防を適応とする。

ポサコナゾール静注用溶液は18歳以上の患者での予防を適応とする。

ポサコナゾール徐放錠及び経口懸濁液は13歳以上の患者での予防を適応とする。

2)　イトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症を含む口腔咽頭カンジダ症の治療

ポサコナゾール経口懸濁液は、イトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症を含む口腔咽頭カンジダ症の治療を適応とする。

用法・用量

1)　ポサコナゾール静注用溶液、徐放錠及び経口懸濁液の重要な使用上の注意

ポサコナゾール徐放錠と経口懸濁液では用法が異なるため、各剤形を置き換えて使用してはならない。

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(1) ポサコナゾール静注用溶液

- 中心静脈カテーテル又は末梢穿刺中心静脈カテーテルを含む中心静脈ラインから、約90分間かけて緩徐に点滴静注すること。
- 中心静脈ライン留置前、中心静脈ラインの位置変更中、又は別の静脈内治療に使用中のため中心静脈カテーテルが利用できない場合は、末梢静脈カテーテルから単回投与として約30分間かけて緩徐に点滴静注してもよい。
- 反復投与が必要な場合は、中心静脈ラインから注入する。
- ポサコナゾール静注用溶液の急速静注は行わないこと。

(2) ポサコナゾール徐放錠

- そのまま飲み込むこと。錠剤を分割したり、砕いたり、かんだりしないこと。
- 食物とともに服用すること。

(3) ポサコナゾール経口懸濁液

- 一回分の食事とともに服用すること。一回分の食事ができない患者では、液体栄養補助剤又は酸性炭酸飲料（例：ジンジャーエール）と同時に服用すること。
- 治療上の有益性が危険性を上回る場合を除き、ポサコナゾールの血漿中濃度を低下させる薬剤との併用は避けること。しかしながら、併用する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。

(4) ポサコナゾール徐放錠及び経口懸濁液

- 重度の下痢又は嘔吐を有する患者にポサコナゾール徐放錠又は経口懸濁液を投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。

2)　ポサコナゾール静注用溶液の用量、調製、静脈ラインの適合性及び用法

(1) 用量

表 1.6-2 ポサコナゾール静注用溶液の用量（原文 Table 1）

適応症	用法・用量
侵襲性アスペルギルス症及び カンジダ症の予防	負荷用量：初日に300 mg を1日2回点滴静注する。 維持用量：2日目以降は300 mg を1日1回点滴静注する。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。

(2) 調製

- 冷蔵保存されていたポサコナゾール静注用溶液のバイアルを室温に戻す。
- 最終濃度がポサコナゾール1 mg/mL～2 mg/mL になるように、1バイアル中（16.7 mL）に充填された静注用溶液（ポサコナゾール300 mg を含む）を無菌下で、適合性が確認

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された混和用希釈液[表 1.6-3]の静注用バッグ（又はボトル）に添加する。その他の希釈液の使用は、粒子形成を引き起こす可能性があるため、推奨しない。

- ポサコナゾール静注用溶液は、保存料を含まない一回使い切りの無菌溶液である。希釈後は速やかに使用すること。速やかに使用しない場合は、2～8°C（36～46°F）で24時間まで冷蔵保存可能である。ポサコナゾール静注用溶液は一回使い切りであり、残液は廃棄すること。
- 非経口製剤は、溶液や容器の濁度がゆるす限り、投与前に目視で異物がないか確認すること。希釈後のポサコナゾール静注用溶液は無色から黄色である。この範囲内の色のばらつきは本剤の品質に影響を及ぼさない。

(3) 希釈液との適合性

ポサコナゾール静注用溶液と注射製剤及び一般的に使用される静注用希釈液との適合性を評価するために、静注器具の側管からの擬似投与試験を実施した。適合性は外観、異物、濁度により評価した。適合性が確認された希釈液及び薬剤をそれぞれ[表 1.6-3]及び[表 1.6-4]に示す。以下に記載されていない希釈液又は薬剤は、ポサコナゾール静注用溶液と同一の静脈ライン（又はカニューレ）から同時に注入しないこと。

- 以下に記載された適合性が確認された希釈液は、ポサコナゾール静注用溶液と同一の静脈ライン（又はカニューレ）から同時に注入可能である。

表 1.6-3 適合性が確認された希釈液（原文 Table 2）

0.45%塩化ナトリウム溶液
0.9%塩化ナトリウム溶液
5%ブドウ糖液
5%ブドウ糖液／0.45%塩化ナトリウム溶液
5%ブドウ糖液／0.9%塩化ナトリウム溶液
5%ブドウ糖液／20ミリ当量塩化カリウム溶液

- 5%ブドウ糖液又は0.9%塩化ナトリウム溶液で調製した以下の薬剤は、ポサコナゾール静注用溶液と同一の静脈ライン（又はカニューレ）から同時に注入可能である。その他の希釈液で調製した薬剤の併用は、粒子形成を引き起こす可能性がある。

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表 1.6-4 適合性が確認された薬剤（原文 Table 3）

アミカシン硫酸塩
カスポファンギン
シプロフロキサシン
ダプトマイシン
ドブタミン塩酸塩
ファモチジン
フィルグラスチム
ゲンタマイシン硫酸塩
ヒドロモルホン塩酸塩
レボフロキサシン
ロラゼパム
メロペネム
ミカファンギン
モルヒネ硫酸塩
酒石酸水素ノルエピネフリン
塩化カリウム
バンコマイシン塩酸塩

(4)　適合性が確認されなかった希釈液

ポサコナゾール静注用溶液は以下の希釈液で希釈してはならない。

- 乳酸リンゲル液
- 5%ブドウ糖加乳酸リンゲル液
- 4.2%炭酸水素ナトリウム溶液

(5)　用法

- ポサコナゾール静注用溶液は、0.22 μm のポリエーテルスルホン又はポリフッ化ビニリデンのフィルターから注入すること。
- 中心静脈カテーテル又は末梢穿刺中心静脈カテーテルを含む中心静脈ラインから、約90分間かけて緩徐に点滴静注すること。ポサコナゾール静注用溶液の急速静注は行わないこと。
- 中心静脈ライン留置前、中心静脈ラインの位置変更中又は別の静脈内治療に使用中のため中心静脈カテーテルが使用できない場合は、末梢静脈カテーテルから単回投与してもよい。
- 反復投与が必要な場合は、中心静脈ラインから注入する。末梢静脈カテーテルから注入する場合、約30分間かけて静注すること。注：臨床試験において、同一の静脈から反復末梢注入された患者に注入部位反応が認められた。

3)　ポサコナゾール徐放錠の用量及び用法

(1)　用量

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表 1.6-5 ポサコナゾール徐放錠の用量（原文 Table 4）

適応症	用法・用量
侵襲性アスペルギルス症及びカンジダ症の予防	負荷用量：初日に300 mg（100 mg 徐放錠3錠）を1日2回服用する。 維持用量：2日目以降は300 mg（100 mg 徐放錠3錠）を1日1回服用する。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。

(2) 用法

- そのまま飲み込むこと。錠剤を分割したり、砕いたり、かんだりしないこと。
- 経口投与によるポサコナゾールの吸収を増加させ、十分な血漿中濃度を確保するため、食物とともにポサコナゾール徐放錠を服用すること。
- ポサコナゾール徐放錠は予防目的としてのみ使用すること。
- ポサコナゾール徐放錠の食後及び空腹時の血漿中濃度は、ポサコナゾール経口懸濁液の同血漿中濃度と比較して概して高いため、予防目的の経口製剤としてはポサコナゾール徐放錠が好ましい。

4)　ポサコナゾール経口懸濁液の用量及び用法

(1) 用量

表 1.6-6 ポサコナゾール経口懸濁液の用量（原文 Table 5）

適応症	用法・用量
侵襲性アスペルギルス症及びカンジダ症の予防	200 mg（5 mL）を1日3回服用する。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。
口腔咽頭カンジダ症の治療	負荷用量：初日に100 mg（2.5 mL）を1日2回服用する。 維持用量：2日目以降は100 mg（2.5 mL）を1日1回13日間服用する。
イトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症の治療	400 mg（10 mL）を1日2回服用する。 投与期間は患者の基礎疾患の程度及び臨床効果に基づき設定すること。

(2) 用法

- ポサコナゾール経口懸濁液は、使用前によく振盪すること。計量スプーンで服用すること[図 1.6-1]。

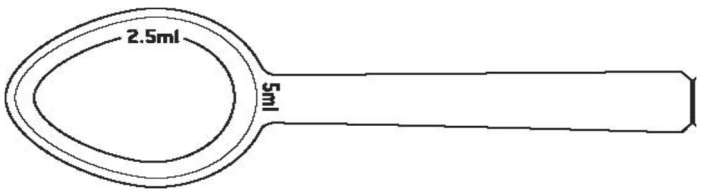


図 1.6-1 計量スプーン（2.5 mL 及び 5 mL の目盛り付き）（原文 Figure 1）

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- 各服用後及び保存前にスプーンを水ですすぐこと。
- 経口投与によるポサコナゾールの吸収を増加させ、十分な血漿中濃度を確保するため、一回分の食事中又は食後すぐ（20分以内）にポサコナゾール経口懸濁液を服用すること。
- 一回分の食事ができない患者では、ポサコナゾール経口懸濁液の代わりにポサコナゾール徐放錠を使用すること。ポサコナゾール徐放錠は予防目的としてのみ使用すること。空腹時では、ポサコナゾール徐放錠の血漿中濃度はポサコナゾール経口懸濁液と比較して高い。
- 一回分の食事ができなく、かつ、ポサコナゾール徐放錠又は静注用溶液が選択できない患者では、ポサコナゾール経口懸濁液と液体栄養補助剤又は酸性炭酸飲料（例：ジンジャーエール）を同時に服用することができる。
- 一回分の食事ができない又は液体栄養補助剤や酸性炭酸飲料を摂取できなく、かつ、ポサコナゾール徐放錠又は静注用溶液が選択できない患者では、代替の抗真菌薬治療を検討する又はブレイクスルー真菌感染の有無を注意深く観察すること。

5)　ポサコナゾール徐放錠及び経口懸濁液に互換性はない

各剤形での用量が異なるため、ポサコナゾール徐放錠と経口懸濁液を置き換えて使用してはならない。したがって、各剤形に特有の推奨用量に従うこと。

6)　腎機能障害を有する患者での用量調整

ポサコナゾール経口懸濁液及び徐放錠の薬物動態は、腎機能障害により大きな影響は受けない。したがって、軽度から重度の腎機能障害を有する患者に対するポサコナゾール経口製剤の用量調整の必要はない。

- 中等度又は重度［推定糸球体濾過量（eGFR）：<50 mL/min］の腎機能障害を有する患者では、患者の有益性及び危険性を考慮して使用が正当化されない限り、ポサコナゾール静注用溶液の投与を避けること。
- 中等度又は重度（eGFR：<50 mL/min）の腎機能障害を有する患者にポサコナゾール静注用溶液を投与した場合、基剤であるスルホブチルエーテルβ-シクロデキストリンナトリウム（SBECD）が蓄積するおそれがある。これらの腎機能障害を有する患者では、血清クレアチニン値を慎重にモニタリングし、増加が認められた場合にはポサコナゾール経口製剤への切り替えを考慮すること。

禁忌

1)　過敏症

ポサコナゾールは、ポサコナゾール又は他のアゾール系抗真菌薬に対して過敏症のある患者には禁忌である。

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2)　シロリムスとの併用

シロリムスとポサコナゾールの併用は禁忌である。シロリムスとポサコナゾールの併用により、シロリムスの血中濃度が約9倍に増加し、シロリムスによる毒性がみられることがある。

3)　CYP3A4基質との併用による QT 延長

QT 延長を引き起こす CYP3A4基質とポサコナゾールの併用は禁忌である。CYP3A4基質であるピモジド及びキニジンとポサコナゾールの併用により、CYP3A4基質の血漿中濃度が増加すると、QTc 延長やトルサード ド ポアントを引き起こすことがある。

4)　CYP3A4を介して主に代謝される HMG-CoA 還元酵素阻害剤

CYP3A4を介して主に代謝される HMG-CoA 還元酵素阻害剤（例：アトルバスタチン、ロバスタチン及びシンバスタチン）とポサコナゾールの併用により、これらの薬剤の血漿中濃度が増加し、横紋筋融解症に至ることがあるため、両薬剤の併用は禁忌である。

5)　麦角アルカロイドとの併用

ポサコナゾールとの併用により麦角アルカロイド(エルゴタミン及びジヒドロエルゴタミン)の血漿中濃度が増加し、麦角中毒を引き起こすことがある。

警告及び使用上の注意

1)　カルシニューリン阻害剤との薬物相互作用

シクロスポリン及びタクロリムスとポサコナゾールの併用により、これらのカルシニューリン阻害剤の全血中トラフ濃度が増加する。臨床薬理試験では、シクロスポリン及びタクロリムスの血中濃度が増加した患者で腎毒性及び白質脳症(致死的な事象を含む)が認められている。ポサコナゾールの併用中及び中止時は、タクロリムス又はシクロスポリンの全血中トラフ濃度を頻回にモニタリングし、それに応じてタクロリムス又はシクロスポリンの用量調整をすること。

2)　不整脈及び QT 延長

ポサコナゾールを含む一部のアゾール系抗真菌薬では、心電図での QT 延長との関連が知られている。また、ポサコナゾールを投与された複数の患者でトルサード ド ポアントが報告されている。

健康被験者で複数の同一時刻に心電図を記録した解析結果からは、QTc 間隔（平均値）の延長は認められなかった。高脂肪食の摂取後にポサコナゾール経口懸濁液400 mg を1日2回投与した173例の健康被験者（18～85歳）で、ベースライン及び定常状態時の複数の同一時刻における心電図を12時間にわたり記録した。本併合解析で、臨床推奨用量投与後の Fridericia 法で補正した QTc［QTc(F)］間隔のベースラインからの平均変化量は-5 msec であった。プラセボが投与された被験者の一部（16例）で、QTc(F)間隔の短縮（-3 msec）が認められた。プラセボで補正し

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た QTc(F)間隔最高値のベースラインからの平均変化量は0 msec 未満（-8 msec）であった。また、ポサコナゾールが投与された被験者で、QTc(F)間隔が500 msec 以上又は QTc(F)間隔がベースラインから60 msec 以上延長した被験者は認められなかった。

催不整脈状態にある患者へのポサコナゾールの投与には注意が必要である。QTc 間隔を延長することが知られ、CYP3A4により代謝される薬剤とポサコナゾールを併用しないこと。ポサコナゾール治療前にカリウム、マグネシウム及びカルシウムの値が適正となるようを厳格に注意すること。

3)　肝毒性

臨床試験では、肝機能障害（例：ALT、AST、ALP 及び総ビリルビンの軽度から中等度の増加、肝炎）が報告されている。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もいた。重篤な基礎疾患（例：血液悪性腫瘍）を有する患者で、ポサコナゾール投与期間中に、胆汁うっ滞又は致死的な肝不全を含む、より重症の肝機能障害が認められた。これらの重症の肝機能障害は、ポサコナゾール経口懸濁液の1日用量800 mg（400 mg 1日2回又は200 mg 1日4回）が投与された臨床試験の患者で主に認められた。

ポサコナゾールによる治療開始前及び治療中は、肝機能検査を実施すること。ポサコナゾールによる治療中に肝機能検査異常を発現した患者では、より重度の肝損傷の発現について観察すること。患者の管理には、肝機能の臨床評価（特に肝機能検査及びビリルビン）を含めること。肝疾患に一致する臨床徴候や症状が現れた場合、ポサコナゾールの中止を考慮すること。

4)　腎機能障害

ポサコナゾール徐放錠及び経口懸濁液では曝露量にばらつきが認められるため、重度の腎機能障害を有する患者に投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。

中等度又は重度（eGFR：<50 mL/min）の腎機能障害を有する患者では、患者の有益性及び危険性を考慮して使用が正当化されない限り、ポサコナゾール静注用溶液の投与を避けること。中等度又は重度の腎機能障害を有する患者にポサコナゾール静注用溶液を投与した場合、基剤であるスルホブチルエーテル β-シクロデキストリンナトリウム（SBECD）が蓄積するおそれがある。これらの腎機能障害を有する患者では、血清クレアチニン値を慎重にモニタリングし、上昇が認められた場合にはポサコナゾール経口製剤への切り替えを考慮すること。

5)　ミダゾラムとの併用

ミダゾラムとポサコナゾールの併用により、ミダゾラムの血漿中濃度が約5倍に増加する。ミダゾラムの血漿中濃度の増加は、催眠及び鎮静作用を促進及び延長するおそれがある。ミダゾラムの血漿中濃度の増加により引き起こされる副作用を注意深く観察し、これらの作用を減弱させるためにベンゾジアゼピン受容体拮抗剤を利用可能にしておくこと。

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6)　ビンクリスチンの毒性

ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

有害事象

1)　重篤又はその他の重要な有害事象

以下の重篤又はその他の重要な有害事象に関する詳細が米国添付文書の別項に記載されている。

- 過敏症
- 不整脈及び QT 延長
- 肝毒性

2)　臨床試験成績

臨床試験は広く様々な条件下で実施されるため、ポサコナゾールの臨床試験で認められた有害事象の発現割合を他剤の臨床試験の発現割合と直接比較することはできない。また、臨床試験で認められた有害事象の発現割合が実際の発現割合と一致しない可能性もある。臨床試験で報告されたポサコナゾール静注用溶液及び徐放錠の有害事象の種類は、ポサコナゾール経口懸濁液で報告されたものと概して同様であった。

(1)　ポサコナゾール静注用溶液の臨床試験成績

末梢静脈カテーテルを介したポサコナゾール静注用溶液の反復投与により血栓性静脈炎が認められた（発現割合：60%）。そのため、その後の試験ではポサコナゾール静注用溶液は中心静脈カテーテルを介して投与された。

患者268例を対象にポサコナゾール静注用溶液の安全性を評価した。患者は真菌症予防を目的としたポサコナゾール静注用溶液の薬物動態及び安全性評価の非対照試験に組み入れられた（ポサコナゾール静注用溶液　試験 1）。患者は血液悪性腫瘍、化学療法後の好中球減少症、移植片対宿主病（GVHD）、造血幹細胞移植（HSCT）後などの基礎疾患を伴う免疫不全状態にあった。この患者集団では、男性55%、平均年齢51歳（範囲：18～82歳、65歳以上：19%）、白人95%、ヒスパニック系8%であった。10例にポサコナゾール静注用溶液200 mg を単回投与、21例に200 mg/日を14日間（中央値）、237例に300 mg/日を9日間（中央値）投与した。

ポサコナゾール静注用溶液の試験において、ポサコナゾール静注用溶液300 mg/日を投与した患者に認められた有害事象の発現例数を[表 1.6-7]に示す。初日には負荷用量300 mgを1日2回投与した。ポサコナゾールを合計28日間投与するため、ポサコナゾールの静脈内

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投与後、ポサコナゾール経口懸濁液を投与した。

表 1.6-7 ポサコナゾール静注用溶液　試験 1
ポサコナゾール静注用溶液 300 mg/日投与患者における
発現割合 10%以上の有害事象の発現例数（%）（原文 Table 6）

器官別大分類 基本語	ポサコナゾール 静注用溶液 投与期 n=237 (%)†		ポサコナゾール静注用溶液投与期又はそれに続く経口懸濁液投与期 n=237(%)‡	
有害事象が認められた患者	220	(93)	235	(99)
血液およびリンパ系障害				
貧血	16	(7)	23	(10)
血小板減少症	17	(7)	25	(11)
胃腸障害				
上腹部痛	15	(6)	25	(11)
腹痛	30	(13)	41	(17)
便秘	18	(8)	31	(13)
下痢	75	(32)	93	(39)
悪心	46	(19)	70	(30)
嘔吐	29	(12)	45	(19)
一般・全身障害および投与部位の状態				
疲労	19	(8)	24	(10)
悪寒	28	(12)	38	(16)
末梢性浮腫	28	(12)	35	(15)
発熱	49	(21)	73	(31)
代謝および栄養障害				
食欲減退	23	(10)	29	(12)
低カリウム血症	51	(22)	67	(28)
低マグネシウム血症	25	(11)	30	(13)
神経系障害				
頭痛	33	(14)	49	(21)
呼吸器、胸郭および縦隔障害				
咳嗽	21	(9)	31	(13)
呼吸困難	16	(7)	24	(10)
鼻出血	34	(14)	40	(17)
皮膚および皮下組織障害				
点状出血	20	(8)	24	(10)
発疹	35	(15)	56	(24)
血管障害				
高血圧	20	(8)	26	(11)

† 本試験のポサコナゾール静脈内投与期間中に患者に認められた有害事象
‡ 本試験のポサコナゾール投与期間中（最長28日間）にいずれかの時点で患者に認められた有害事象

ポサコナゾール300 mg 1日1回の静脈内投与で認められた有害事象で発現割合が高い事象は、下痢（32%）、低カリウム血症（22%）、発熱（21%）及び悪心（19%）であった。これらの有害事象は、ポサコナゾール経口懸濁液の試験で認められた有害事象と同様であった。

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(2)　ポサコナゾール徐放錠の臨床試験成績

患者230例を対象にポサコナゾール徐放錠の安全性を評価した。患者は真菌症予防を目的としたポサコナゾール徐放錠の薬物動態及び安全性評価の非対照試験に組み入れられた（ポサコナゾール徐放錠　試験1）。患者は血液悪性腫瘍、化学療法後の好中球減少症、GVHD、HSCT 後などの基礎疾患を伴う免疫不全状態にあった。この患者集団では、男性62%、平均年齢51歳（範囲：19～78歳、65歳以上：17%）、白人93%、ヒスパニック系16%であった。ポサコナゾールの投与期間の中央値は28日間であった。20例に200 mg/日、210例に300 mg/日を投与した（各コホートとも初日は1日2回）。ポサコナゾール徐放錠の試験において、ポサコナゾール徐放錠300 mg/日を投与した患者に認められた発現割合10%以上の有害事象の発現例数を[表 1.6-8]に示す。

表 1.6-8 ポサコナゾール徐放錠　試験 1
ポサコナゾール徐放錠 300 mg/日投与患者における
発現割合 10%以上の有害事象の発現例数（%）（原文 Table 7）

器官別大分類 基本語	ポサコナゾール徐放錠（300 mg） (n=210)	
有害事象が認められた患者	201	(99)
血液およびリンパ系障害		
貧血	22	(10)
血小板減少症	29	(14)
胃腸障害		
腹痛	23	(11)
便秘	20	(10)
下痢	61	(29)
悪心	56	(27)
嘔吐	28	(13)
一般・全身障害および投与部位の状態		
無力症	20	(10)
悪寒	22	(10)
粘膜の炎症	29	(14)
末梢性浮腫	33	(16)
発熱	59	(28)
代謝および栄養障害		
低カリウム血症	46	(22)
低マグネシウム血症	20	(10)
神経系障害		
頭痛	30	(14)
呼吸器、胸郭および縦隔障害		
咳嗽	35	(17)
鼻出血	30	(14)
皮膚および皮下組織障害		
発疹	34	(16)
血管障害		
高血圧	23	(11)

ポサコナゾール徐放錠300 mg 1日1回服用で認められた有害事象で発現割合が高い（25%

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超）事象は、下痢、発熱及び悪心であった。

ポサコナゾール徐放錠300 mg 1日1回服用で投与中止に至った有害事象で発現割合が最も高い事象は、悪心（2%）であった。

(3) ポサコナゾール経口懸濁液の安全性に関する臨床試験成績

患者1,844例を対象にポサコナゾール経口懸濁液の安全性を評価した。その内訳は、実薬対照による予防投与試験の605例、口腔咽頭カンジダ症を対象とした実薬対照試験の557例、難治性口腔咽頭カンジダ症を対象とした試験の239例、その他の適応症を対象とした試験の443例であった。患者集団は多様であり、血液悪性腫瘍、化学療法後の好中球減少症、GVHD、HSCT 後、HIV 感染などの免疫不全状態の他、好中球減少症を伴わない患者も含まれた。この患者集団では、男性71%、平均年齢42歳（範囲：8～84歳、65歳以上：6%、18歳未満：1%）、白人64%、ヒスパニック系16%、非白人36%（黒人14%を含む）であった。ポサコナゾールを171例に6ヵ月以上、58例に12ヵ月以上投与した。ポサコナゾール予防投与試験で発現割合10%以上の有害事象の発現例数を［表 1.6-9］に示す。口腔咽頭カンジダ症又は難治性口腔咽頭カンジダ症を対象とした試験で発現割合10%以上の有害事象の発現例数を[表 1.6-10]に示す。

i. アスペルギルス症及びカンジダ症の予防

ポサコナゾールの予防投与を評価した2つの無作為化比較対照試験（経口懸濁液試験1及び試験2）では、重度免疫不全患者を対象としてポサコナゾール経口懸濁液200 mg 1日3回服用の安全性をフルコナゾール400 mg 1日1回又はイトラコナゾール200 mg 1日2回服用と比較した。

予防投与試験で認められた有害事象で発現割合が高い（30%超）事象は、発熱、下痢及び悪心であった。

予防投与試験でポサコナゾールの投与中止に至った有害事象で発現割合が高い事象は胃腸障害であり、個々の事象は悪心（2%）、嘔吐（2%）及び肝酵素上昇（2%）であった。

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表 1.6-9 ポサコナゾール経口懸濁液　試験 1 及び試験 2
ポサコナゾール経口懸濁液群又はフルコナゾール群における
発現割合 10%以上の有害事象の発現例数（%）
（予防投与試験の安全性併合解析）（原文 Table 8）

器官別大分類 基本語	ポサコナゾール (n=605)		フルコナゾール (n=539)		イトラコナゾール (n=58)	
有害事象が認められた患者	595	(98)	531	(99)	58	(100)
一般的全身障害						
発熱	274	(45)	254	(47)	32	(55)
頭痛	171	(28)	141	(26)	23	(40)
悪寒	122	(20)	87	(16)	17	(29)
疲労	101	(17)	98	(18)	5	(9)
下肢浮腫	93	(15)	67	(12)	11	(19)
食欲不振	92	(15)	94	(17)	16	(28)
浮動性めまい	64	(11)	56	(10)	5	(9)
浮腫	54	(9)	68	(13)	8	(14)
脱力	51	(8)	52	(10)	2	(3)
心・血管障害（一般）						
高血圧	106	(18)	88	(16)	3	(5)
低血圧	83	(14)	79	(15)	10	(17)
血液およびリンパ系障害						
貧血	149	(25)	124	(23)	16	(28)
好中球減少症	141	(23)	122	(23)	23	(40)
生殖系および乳房障害						
膣出血†	24	(10)	20	(9)	3	(12)
胃腸障害						
下痢	256	(42)	212	(39)	35	(60)
悪心	232	(38)	198	(37)	30	(52)
嘔吐	174	(29)	173	(32)	24	(41)
腹痛	161	(27)	147	(27)	21	(36)
便秘	126	(21)	94	(17)	10	(17)
消化不良	61	(10)	50	(9)	6	(10)
心拍数・心リズム障害						
頻脈	72	(12)	75	(14)	3	(5)
感染症および寄生虫症						
咽頭炎	71	(12)	60	(11)	12	(21)
肝臓・胆管系障害						
ビリルビン血症	59	(10)	51	(9)	11	(19)
代謝・栄養障害						
低カリウム血症	181	(30)	142	(26)	30	(52)
低マグネシウム血症	110	(18)	84	(16)	11	(19)
高血糖	68	(11)	76	(14)	2	(3)
低カルシウム血症	56	(9)	55	(10)	5	(9)
筋・骨格系障害						
筋骨格痛	95	(16)	82	(15)	9	(16)
関節痛	69	(11)	67	(12)	5	(9)
背部痛	63	(10)	66	(12)	4	(7)
血小板・出血凝血障害						
血小板減少症	175	(29)	146	(27)	20	(34)
点状出血	64	(11)	54	(10)	9	(16)
精神障害						
不眠症	103	(17)	92	(17)	11	(19)
呼吸器系障害						
咳嗽	146	(24)	130	(24)	14	(24)
呼吸困難	121	(20)	116	(22)	15	(26)

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表 1.6-9　　ポサコナゾール経口懸濁液　試験1及び試験2
ポサコナゾール経口懸濁液群又はフルコナゾール群における
発現割合10%以上の有害事象の発現例数（%）
（予防投与試験の安全性併合解析）（原文 Table 8）（続き）

器官別大分類 基本語	ポサコナゾール (n=605)		フルコナゾール (n=539)		イトラコナゾール (n=58)	
鼻出血	82	(14)	73	(14)	12	(21)
皮膚・皮膚付属器障害						
発疹	113	(19)	96	(18)	25	(43)
そう痒症	69	(11)	62	(12)	11	(19)
† 性別特有の有害事象では各性別の患者数に基づいて発現割合を算出した。						

ii.　　口腔咽頭カンジダ症を有する HIV 感染患者

口腔咽頭カンジダ症を対象とした2つの無作為化比較対照試験では、HIV 感染患者557例へのポサコナゾール経口懸濁液400 mg 以下の1日1回服用の安全性を HIV 感染患者262例へのフルコナゾール100 mg を1日1回服用と比較した。

また、難治性口腔咽頭カンジダ症を対象とした2つの非対照試験では、難治性口腔咽頭カンジダ症を有する HIV 感染患者239例にポサコナゾール経口懸濁液を投与した。このうち、149例に800 mg/日、残りの患者に400 mg 以下を1日1回投与した。

口腔咽頭カンジダ症及び難治性口腔咽頭カンジダ症を対象としたこれらの試験で認められた有害事象で発現割合が高い事象は、発熱、下痢、悪心、頭痛、嘔吐及び咳嗽であった。

口腔咽頭カンジダ症の比較試験併合群における、ポサコナゾールの投与中止に至った有害事象で発現割合が高い事象は、呼吸器障害（1%）及び肺炎（1%）であった。難治性口腔咽頭カンジダ症の試験併合群でポサコナゾールの投与中止に至った有害事象で発現割合が高い事象は、AIDS（7%）及び呼吸器障害（3%）であった。

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表 1.6-10　　ポサコナゾール経口懸濁液を投与された
口腔咽頭カンジダ症患者における
発現割合 10%以上の有害事象の発現例数（治験薬投与集団）（原文 Table 9）

器官別大分類 基本語	患者数（%）					
	OPC 比較試験データの併合				難治性 OPC 試験データの併合	
	ポサコナゾール		フルコナゾール		ポサコナゾール	
	n=557		n=262		n=239	
有害事象が認められた患者†	356	(64)	175	(67)	221	(92)
一般的全身障害						
発熱	34	(6)	22	(8)	82	(34)
頭痛	44	(8)	23	(9)	47	(20)
食欲不振	10	(2)	4	(2)	46	(19)
疲労	18	(3)	12	(5)	31	(13)
無力症	9	(2)	5	(2)	31	(13)
悪寒	2	(<1)	4	(2)	29	(12)
疼痛	4	(1)	2	(1)	27	(11)
血液およびリンパ系障害						
好中球減少症	21	(4)	8	(3)	39	(16)
貧血	11	(2)	5	(2)	34	(14)
胃腸障害						
下痢	58	(10)	34	(13)	70	(29)
悪心	48	(9)	30	(11)	70	(29)
嘔吐	37	(7)	18	(7)	67	(28)
腹痛	27	(5)	17	(6)	43	(18)
感染症および寄生虫症						
口腔カンジダ症	3	(1)	1	(<1)	28	(12)
単純ヘルペス	16	(3)	8	(3)	26	(11)
肺炎	17	(3)	6	(2)	25	(10)
代謝・栄養障害						
体重減少	4	(1)	2	(1)	33	(14)
脱水	4	(1)	7	(3)	27	(11)
精神障害						
不眠症	8	(1)	3	(1)	39	(16)
呼吸器系障害						
咳嗽	18	(3)	11	(4)	60	(25)
呼吸困難	8	(1)	8	(3)	28	(12)
皮膚・皮膚付属器障害						
発疹	15	(3)	10	(4)	36	(15)
多汗	13	(2)	5	(2)	23	(10)

OPC：口腔咽頭カンジダ症
† 試験期間中に有害事象（投与との因果関係は問わない）が1件以上認められた患者数。事象が複数回認められた患者がいる可能性もある。

有害事象の発現割合は難治性口腔咽頭カンジダ症の試験併合群で高かった。これらの進行した HIV 疾患を有する重度免疫不全患者のうち、重篤な有害事象は 55%（132/239例）に認められた。発現割合が高い重篤な有害事象は、発熱（13%）及び好中球減少症（10%）であった。

iii.　　発現割合が低い有害事象

予防投与試験、口腔咽頭カンジダ症及び難治性口腔咽頭カンジダ症を対象とし

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た試験又はポサコナゾールの他の試験で認められた、発現割合5%未満の臨床的に重要な有害事象を以下に示す。

- 血液及びリンパ系障害：溶血性尿毒症症候群、血栓性血小板減少性紫斑病、好中球減少症増悪
- 内分泌障害：副腎機能不全
- 神経系障害：錯感覚
- 免疫系障害：アレルギー反応
- 心臓障害：トルサード ド ポアント
- 血管障害：肺塞栓症
- 胃腸障害：膵炎
- 肝胆道系障害：ビリルビン血症、肝酵素上昇、肝機能異常、肝炎、肝腫大、黄疸、AST 増加、ALT 増加
- 代謝及び栄養障害：低カリウム血症
- 血小板、出血及び凝固障害：血小板減少症
- 腎及び尿路障害：急性腎不全

iv.　臨床検査値

健康被験者及び患者で認められた肝機能検査値の上昇は血漿中ポサコナゾール濃度の高値と関連しないと考えられた。

予防投与試験で共通毒性基準（CTC）に基づく肝機能検査値が、ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数を[表1.6-11]に示す。

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表 1.6-11　　ポサコナゾール経口懸濁液　試験 1 及び試験 2
肝機能検査値がベースライン時の CTC Grade 0、1 又は 2 から
Grade 3 又は 4 へ変化した例数（原文 Table 10）

変化が認められた患者数（%）† 経口懸濁液　試験1				
臨床検査値	ポサコナゾール n=301		フルコナゾール n=299	
AST	11/266	(4)	13/266	(5)
ALT	47/271	(17)	39/272	(14)
ビリルビン	24/271	(9)	20/275	(7)
ALP	9/271	(3)	8/271	(3)
経口懸濁液　試験2				
臨床検査値	ポサコナゾール n=304		フルコナゾール／イトラコナゾール n=298	
AST	9/286	(3)	5/280	(2)
ALT	18/289	(6)	13/284	(5)
ビリルビン	20/290	(7)	25/285	(9)
ALP	4/281	(1)	1/276	(<1)

† ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数。X はその定義を満たす患者数、Y はベースライン値が得られ、かつベースライン後の1時点以上で検査値が得られた患者数として、X/Y の形式でデータを示す。
CTC：共通毒性基準、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、ALP：アルカリホスファターゼ

投与を受けた口腔咽頭カンジダ症患者のうち、試験期間中に臨床的に意義のある肝機能検査異常が認められた患者数を[表 1.6-12]に示す（これらの患者の一部では、治験薬の投与開始前に臨床検査異常が認められた）。

表 1.6-12　　ポサコナゾール経口懸濁液の試験
臨床的に意義のある肝機能検査異常
（ベースライン値を問わない異常値）（原文 Table 11）

臨床検査値	OPC 比較試験データの併合				難治性 OPC 試験データの併合	
	ポサコナゾール		フルコナゾール		ポサコナゾール	
	n=557		n=262		n=239	
ALT>3.0×ULN	16/537	(3)	13/254	(5)	25/226	(11)
AST>3.0×ULN	33/537	(6)	26/254	(10)	39/223	(17)
総ビリルビン>1.5×ULN	15/536	(3)	5/254	(2)	9/197	(5)
ALP>3.0×ULN	17/535	(3)	15/253	(6)	24/190	(13)

OPC：口腔咽頭カンジダ症、ALT：アラニンアミノトランスフェラーゼ、ULN：基準値上限、AST：アスパラギン酸アミノトランスフェラーゼ、ALP：アルカリホスファターゼ

3)　製造販売後の使用経験

臨床試験では認められず、製造販売後に報告された副作用には、臨床的に意義のある事象は特定されていない。

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薬物相互作用

ポサコナゾールは主にウリジン5'-二リン酸-グルクロン酸転移酵素（UGT）を介して代謝され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程を阻害又は誘導する薬剤により、血漿中ポサコナゾール濃度が影響される可能性がある。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールの血漿中濃度を低下させる薬剤との併用は避けること。ポサコナゾールとの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察すること。

ポサコナゾールは CYP3A4の強力な阻害剤である。したがって、主に CYP3A4により代謝される薬剤は、ポサコナゾールとの併用により血漿中濃度が増加する可能性がある。

以下の情報は、ポサコナゾール経口懸濁液又は初期の錠剤のデータから得られたものである。ポサコナゾールの吸収に影響を及ぼす薬剤（胃内 pH 又は胃運動に影響を及ぼす薬剤）を除き、ポサコナゾール経口懸濁液で起こる薬物相互作用はポサコナゾール静注用溶液でも同様に起こると考えられる。

1)　CYP3A4により代謝される免疫抑制薬

(1)　シロリムス

ポサコナゾールとの併用によりシロリムスの血中濃度が約9倍に増加し、シロリムスの毒性を引き起こす可能性がある。したがって、シロリムスとポサコナゾールの併用は禁忌である。

(2)　タクロリムス

タクロリムスを処方されている患者にポサコナゾールを投与した際、タクロリムスの C_{max} 及び AUC が顕著に増加した。ポサコナゾールによる治療を開始する際は、タクロリムスの用量をそれまでの約1/3に減量すべきである。ポサコナゾールの併用期間中及び中止する際は、タクロリムスの全血中トラフ濃度を頻回にモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(3)　シクロスポリン

シクロスポリンを処方されていた心臓移植患者にポサコナゾールを投与した際、シクロスポリンの全血中濃度が増加した。ポサコナゾールによる治療を開始する際は、シクロスポリンの用量をそれまでの約3/4に減量すべきである。ポサコナゾールの併用期間中及び中止する際は、シクロスポリンの全血中トラフ濃度を頻回にモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

2)　CYP3A4基質

ピモジドやキニジン等の CYP3A4基質とポサコナゾールの併用により、これらの血漿中濃度が増加し、QTc 延長やトルサード ド ポアントを引き起こすことがある。したがって、CYP3A4

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基質とポサコナゾールの併用は禁忌である。

3)　主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤（スタチン）

シンバスタチンとポサコナゾールの併用により、シンバスタチンの血漿中濃度が約10倍に増加する。したがって、主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤とポサコナゾールの併用は禁忌である。

4)　麦角アルカロイド

ほとんどの麦角アルカロイドは CYP3A4の基質である。ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こす可能性がある。したがって、麦角アルカロイドとポサコナゾールの併用は禁忌である。

5)　CYP3A4により代謝されるベンゾジアゼピン系薬剤

ミダゾラムとポサコナゾールの併用により、ミダゾラムの血漿中濃度が約5倍に増加する。ミダゾラムの血漿中濃度の増加は、催眠及び鎮静作用を促進及び延長するおそれがある。CYP3A4により代謝されるその他のベンゾジアゼピン系薬剤（例：アルプラゾラム、トリアゾラム）とポサコナゾールの併用は、これらのベンゾジアゼピン系薬剤の血漿中濃度を増加させる可能性がある。CYP3A4により代謝されるベンゾジアゼピン系薬剤の血漿中濃度の増加により引き起こされる副作用を注意深く観察し、これらの作用を減弱させるためにベンゾジアゼピン受容体拮抗剤を利用可能にしておくこと。

6)　抗 HIV 薬

エファビレンツ：エファビレンツはウリジン5’-二リン酸-グルクロン酸転移酵素を誘導し、ポサコナゾールの血漿中濃度を著しく低下させる。治療上の有益性が危険性を上回る場合を除き、エファビレンツとポサコナゾールの併用は避けること。

リトナビル及びアタザナビル：リトナビル及びアタザナビルは CYP3A4によって代謝され、ポサコナゾールはこれらの血漿中濃度を増加させる。リトナビル及びアタザナビルとポサコナゾールの併用時は、有害事象並びにリトナビル及びアタザナビルの毒性を頻回にモニタリングすること。

ホスアンプレナビル：ホスアンプレナビルとポサコナゾールの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ホスアンプレナビルとポサコナゾールの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。

7)　リファブチン

リファブチンはウリジン5’-二リン酸-グルクロン酸転移酵素を誘導し、ポサコナゾールの血漿中濃度を低下させる。また、リファブチンは CYP3A4によって代謝される。したがって、リフ

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ァブチンとポサコナゾールの併用は、リファブチンの血漿中濃度を増加させる。治療上の有益性が危険性を上回る場合を除き、リファブチンとポサコナゾールの併用は避けること。リファブチンとポサコナゾールの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察し、全血球数及びリファブチンの血漿中濃度の増加に起因する副作用（例：ぶどう膜炎、白血球減少症）を頻回にモニタリングすることを推奨する。

8)　フェニトイン

フェニトインはウリジン5’-二リン酸-グルクロン酸転移酵素を誘導し、ポサコナゾールの血漿中濃度を低下させる。また、フェニトインは CYP3A4によって代謝される。したがって、フェニトインとポサコナゾールの併用は、フェニトインの血漿中濃度を増加させる。治療上の有益性が危険性を上回る場合を除き、フェニトインとポサコナゾールの併用は避けること。フェニトインとポサコナゾールの併用が必要な場合は、フェニトインの減量を検討するとともに、ブレイクスルー真菌感染の有無を注意深く観察し、フェニトインの血漿中濃度の頻回にモニタリングすること。

9)　制酸剤／中和剤

(1)　ポサコナゾール徐放錠

制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬をポサコナゾール徐放錠と併用しても、ポサコナゾールの薬物動態に臨床的に意義のある影響は認められなかった。したがって、制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬との併用に際し、ポサコナゾール徐放錠の用量調整の必要はない。

(2)　ポサコナゾール経口懸濁液

ポサコナゾール経口懸濁液とシメチジン（H_2受容体拮抗薬）及びエソメプラゾール（プロトンポンプ阻害薬）との併用により、ポサコナゾールの血漿中濃度が低下する。治療上の有益性が危険性を上回る場合を除き、シメチジン及びエソメプラゾールとポサコナゾール経口懸濁液の併用は避けること。ポサコナゾールとの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。

ポサコナゾール経口懸濁液と制酸剤及びシメチジンを除く H_2受容体拮抗薬を併用しても、臨床的に意義のある影響は認められなかった。したがって、制酸剤及びシメチジンを除く H_2受容体拮抗薬との併用に際し、ポサコナゾール経口懸濁液の用量調整の必要はない。

10)　ビンカアルカロイド

ビンカアルカロイドの大半（例：ビンクリスチン、ビンブラスチン）は CYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な有害事象を引き起こすおそれがあることが知られている。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。この

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ため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

11) CYP3A4により代謝されるカルシウムチャネル遮断薬

ポサコナゾールは CYP3A4により代謝されるカルシウムチャネル遮断薬（例：ベラパミル、ジルチアゼム、ニフェジピン、ニカルジピン、フェロジピン）の血漿中濃度を増加させる可能性がある。ポサコナゾールとの併用期間中、カルシウムチャネル遮断薬に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を減量すること。

12) ジゴキシン

ジゴキシンとポサコナゾールの併用により、ジゴキシンの血漿中濃度が増加することが報告されている。したがって、ポサコナゾールと併用する場合、ジゴキシンの血漿中濃度をモニタリングすることを推奨する。

13) 胃運動に影響を及ぼす薬剤

(1) ポサコナゾール徐放錠

ポサコナゾール徐放錠とメトクロプラミドを併用しても、ポサコナゾールの薬物動態に影響は認められなかった。メトクロプラミドとポサコナゾールを併用する場合は、ポサコナゾール徐放錠の用量調整の必要はない。

(2) ポサコナゾール経口懸濁液

ポサコナゾール経口懸濁液とメトクロプラミドの併用により、ポサコナゾールの血漿中濃度は低下する。メトクロプラミドと併用する場合、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。

ポサコナゾール経口懸濁液とロペラミドは併用しても、ポサコナゾールの血漿中濃度に影響を及ぼさない。ロペラミドとポサコナゾールを併用する場合、ポサコナゾール経口懸濁液の用量調整の必要はない。

14) Glipizide

Glipizide とポサコナゾールの併用時は、glipizide の用量調整の必要はないが、グルコースの血中濃度をモニタリングすることを推奨する。

特殊集団への投与

1)　妊娠

妊婦を対象にして、適切かつ十分に管理した試験は実施していない。妊娠中のポサコナゾールの使用は、母親の治療上の有益性が胎児への危険性を明らかに上回ると判断する場合のみ使用すること。

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骨格奇形（頭蓋奇形及び肋骨欠損）が27 mg/kg 以上（健康被験者にポサコナゾール経口懸濁液400 mg 1日2回投与時の定常状態における曝露量の1.4倍以上）を経口投与したラットで認められた。ラットでの奇形発生の無作用量はポサコナゾール経口懸濁液400 mg 1日2回投与時の曝露量の0.7倍である9 mg/kg であった。ウサギに最高80 mg/kg 投与したとき、奇形は認められなかった。ウサギでの無作用量は20 mg/kg であり、ポサコナゾール経口懸濁液400 mg 1日2回投与時の曝露量のそれぞれ2.9及び5.2倍である40 mg/kg 及び80 mg/kg の高用量では再吸収の増加が認められた。ウサギに80 mg/kg を投与したとき、雌の体重増加の低下及び産児数の減少が認められた。

2)　授乳婦

ポサコナゾールはラットにおいて授乳中の乳汁中に排泄される。ヒト乳汁中へのポサコナゾールの移行は不明である。乳児に重篤な副作用が発現する潜在的な可能性があるため、母親の治療上の有益性を考慮した上で､授乳を中止するかポサコナゾールを中止するか判断すること。

3)　小児への投与

ポサコナゾール静注用溶液の安全性及び有効性は18歳未満の小児患者で確立されていない。非臨床試験での毒性所見から、ポサコナゾール静注用溶液は小児患者に投与しないこと。

ポサコナゾール経口懸濁液及び徐放錠の安全性及び有効性が13～17歳の患者で確立されている。13～17歳の患者に対するポサコナゾールの投与は、適切かつ十分に管理したポサコナゾールの成人を対象とした試験で得られたエビデンスによって支持される。13歳未満（出生～12歳）の患者ではポサコナゾールの安全性及び有効性は確立されていない。

侵襲性真菌症の予防のため13～17歳の患者12例にポサコナゾール経口懸濁液600 mg/日（200 mg 1日3回）を投与した。これら18歳未満の患者における安全性プロファイルは、成人と同様であった。これらのうち10例における定常状態でのポサコナゾール平均血漿中濃度（C_{avg}）は、成人（18歳以上）における C_{avg} と同様であった。好中球減少症の11ヵ月～18歳未満の小児患者136例にポサコナゾール経口懸濁液を投与した試験において、定常状態の C_{avg} が500 ng/mL から2,500 ng/mL 未満を達成した割合は､事前に設定した90%ではなく､約50%の患者であった。

4)　高齢者への投与

ポサコナゾール静注用溶液を投与した279例中52例（19%）が65歳超であった。ポサコナゾール静注用溶液の薬物動態は、若年被験者と高齢被験者で類似している。高齢患者と若年患者で認められた安全性に全般的に違いはなかったため、高齢患者に対する用量調整の推奨はない。

ポサコナゾール徐放錠を投与した230例中38例（17%）が65歳超であった。ポサコナゾール徐放錠の薬物動態は、若年被験者と高齢被験者で類似している。高齢患者と若年患者で認められた安全性に全般的に違いはなかったため、高齢患者に対する用量調整の推奨はない。

予防試験でポサコナゾール経口懸濁液を投与した605例中63例（10%）が65歳超であった。また､別の適応症でポサコナゾール800 mg/日以上を投与された48例が65歳以上であった。高齢患

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者と若年患者で認められた安全性に全般的に違いはなかった。

ポサコナゾール経口懸濁液の薬物動態は、若年被験者と高齢被験者（65歳以上）で類似している。したがって、高齢患者に対してポサコナゾール経口懸濁液を用量調整する必要はない。

臨床試験におけるポサコナゾールの薬物動態及び安全性は、若年被験者と高齢被験者で全般的に違いはなかったが、一部の高齢患者で感度が高くなる可能性は否定できない。

5)　腎機能障害を有する患者への投与

軽度（eGFR：50～80 mL/min/1.73 m^2、6例）及び中等度（eGFR：20～49 mL/min/1.73 m^2、6例）の腎機能障害を有する患者を対象としたポサコナゾール経口懸濁液400 mg の単回経口投与の結果、ポサコナゾールの薬物動態に対する腎機能障害の影響は認められなかった。したがって、軽度及び中等度の腎機能障害を有する患者への用量調整の必要はない。重度（eGFR：<20 mL/min/1.73 m^2）の腎機能障害においても、平均血漿中曝露量（AUC）は正常（eGFR：>80 mL/min/1.73 m^2）な腎機能を有する被験者と同様であった。しかしながら、重度の腎機能障害を有する患者では、他の腎機能障害を有する患者での曝露量（<40% CV）と比べてポサコナゾールの曝露量に大きなばらつき（96% CV）が認められた。曝露量にばらつきが認められるため、重度の腎機能障害を有する患者に投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。ポサコナゾール徐放錠でも同様の取り扱いを推奨するが、ポサコナゾール徐放錠でそのような試験は実施していない。

中等度又は重度（eGFR：<50 mL/min）の腎機能障害を有する患者では、患者の有益性及び危険性を考慮して使用が正当化されない限り、ポサコナゾール静注用溶液の投与を避けること。中等度又は重度（eGFR：<50 mL/min）の腎機能障害を有する患者にポサコナゾール静注用溶液を投与した場合、基剤である SBECD が蓄積するおそれがある。これらの腎機能障害を有する患者では、血清クレアチニン値を慎重にモニタリングし、上昇が認められた場合にはポサコナゾール経口製剤への切り替えを考慮すること。

6)　肝機能障害を有する患者への投与

軽度（Child-Pugh クラス A：6例）、中等度（Child-Pugh クラス B：6例）又は重度（Child-Pugh クラス C：6例）の肝機能障害を有する患者を対象とするポサコナゾール経口懸濁液400 mg の単回経口投与試験の結果、平均 AUC 値は正常な肝機能を有する被験者（18例）と比較して、軽度で43%、中等度で27%、重度で21%高かった。また、平均 C_{max} は、肝機能が正常な被験者より軽度で1%、中等度で40%高く、重度では34%低かった。見かけの全身クリアランス（CL/F）の平均値は、肝機能が正常な被験者と比較して軽度で18%、中等度で36%、重度で28%低かった。消失半減期（$t_{1/2}$）は、肝機能が正常な被験者で27時間、軽度で39時間、中等度で27時間、重度で43時間であった。

軽度から重度の肝機能障害（Child-Pugh クラス A、B 又は C）を有する患者での用量調整の必要はない。ポサコナゾール徐放錠でも同様の取り扱いを推奨するが、ポサコナゾール徐放錠でそのような試験は実施していない。

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また、ポサコナゾール静注用溶液でも同様に推奨するが、ポサコナゾール静注用溶液でそのような試験は実施していない。

7)　性別

ポサコナゾールの薬物動態は、男性と女性で類似している。性別による用量調整の必要はない。

8)　人種

ポサコナゾールの薬物動態は、人種の違いによる大きな影響はない。人種の違いによる用量調整の必要はない。

9)　体重

ポサコナゾール徐放錠の薬物動態モデルからは、体重が120 kg を超える患者ではポサコナゾールの曝露量が低くなる可能性が示唆された。したがって、体重が120 kg を超える患者では、ブレイクスルー真菌感染の有無を注意深く観察すること。

過量投与

ポサコナゾール静注用溶液及び徐放錠の過量投与は報告されていない。

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された患者で発現した有害事象は、より低用量で認められたものと同様であった。

また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

ポサコナゾールは血液透析で除去されない。

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1.6.2.1.2　欧州連合添付文書の概要（和訳）

1.6.2.1.2.1　経口懸濁液

販売名

Noxafil 40 mg/mL 経口懸濁液

剤形・含量

1 mL 中に40 mg のポサコナゾールを含有する白色の懸濁液
懸濁液5 mL 中に約1.75 g のブドウ糖を添加剤として含む

効能・効果

ポサコナゾール経口懸濁液には、成人における以下の真菌症の治療の適応がある：

1) アムホテリシン B 及びイトラコナゾールが無効又は不耐容の患者における侵襲性アスペルギルス症
2) アムホテリシン B が無効又は不耐容の患者におけるフサリウム症
3) イトラコナゾールが無効又は不耐容の患者におけるクロモブラストミコーシス及び菌腫
4) アムホテリシン B、イトラコナゾール及びフルコナゾールが無効又は不耐容の患者におけるコクシジオイデス症
5) 局所療法が無効と予測される、重度疾患を有する又は免疫不全状態の患者における口腔咽頭カンジダ症の一次療法

無効とは、効果がある抗真菌薬を治療用量で最短7日間投与後、感染進行したこと又は改善がみられないことと定義する。

ポサコナゾール経口懸濁液には、以下の患者における侵襲性真菌症の予防の適応もある：

1) 寛解導入化学療法施行中の急性骨髄性白血病（AML）又は骨髄異形成症候群（MDS）患者で、好中球減少症が遷延することが予測され、侵襲性真菌症を発症するリスクが高い患者
2) 移植片対宿主病に対し高用量免疫抑制療法を行う造血幹細胞移植（HSCT）患者で、侵襲性真菌症を発症するリスクが高い患者

用法・用量

ポサコナゾール腸溶錠とポサコナゾール経口懸濁液に互換性はない。

ポサコナゾール腸溶錠と経口懸濁液では、投与頻度、服薬時の食事摂取の条件及び得られる血漿中濃度に違いがあるため、各剤形を置き換えて使用してはならない。したがって、各剤形の用法・用量に従うこと。

ポサコナゾールでの治療は、真菌症管理の経験、又はポサコナゾールが予防投与の適応とする

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疾患のリスクが高い患者での支持療法の経験がある医師によって開始されるべきである。

1)　用量

ポサコナゾールには、他に100 mg 腸溶錠及び300 mg 静注用濃厚溶液がある。ポサコナゾール腸溶錠は、ポサコナゾール経口懸濁液よりも概して高い血漿中濃度を示し、最適な血漿中濃度のために好ましい剤形である。

適応症による推奨用量を[表 1.6-13]に示す。

表 1.6-13　　適応症による推奨用量（原文 Table 1）

適応症	用法・用量
難治性侵襲性真菌症（IFI）／一次療法に不耐容の IFI の治療	200 mg（5 mL）を1日4回服用する。食事や栄養補助剤を摂取可能な場合、食事や栄養補助剤の摂取中又は摂取後、速やかに400 mg（10 mL）を1日2回服用する。投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。
口腔咽頭カンジダ症の治療	初日に200 mg（5 mL）を1日1回、その後は100 mg（2.5 mL）を1日1回13日間服用する。 経口吸収を高めて十分な曝露量を確保するために、ポサコナゾールは食事（摂食困難な場合は栄養補助剤の摂取）中又は食後すぐに服用する。
侵襲性真菌症の予防	200 mg（5 mL）を1日3回服用する。経口吸収を高めて十分な曝露量を確保するために、ポサコナゾールは食事（摂食困難な場合は栄養補助剤の摂取）中又は食後すぐに服用する。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。 AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する。

2)　特殊集団への投与

(1)　腎機能障害を有する患者への投与

ポサコナゾールの薬物動態に及ぼす腎機能障害の影響は認められず、用量調整は必要としない。

(2)　肝機能障害を有する患者への投与

ポサコナゾールの薬物動態に及ぼす肝機能障害（慢性肝疾患の Child-Pugh クラス C を含む）の影響についての限られたデータからは、正常な肝機能を有する被験者と比較して血漿中濃度が高かったが、用量調整の必要性を示唆するものではなかった。血漿中濃度が増加する可能性があるため、注意喚起することを推奨する。

(3)　小児への投与

18歳未満の小児に対するポサコナゾールの安全性及び有効性は確立していない。現在得られている情報は薬理学の項†に記載したが、18歳未満の小児に対する推奨用量は設定できない。

† [1.6.2.2.2.1項]の原文を参照すること。

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3)　投与方法

経口用

ポサコナゾール経口懸濁液は、使用前によく振盪すること。

禁忌

本薬又は本剤の成分に対して過敏症のある患者には禁忌である。

麦角アルカロイドとの併用は禁忌である。

CYP3A4基質のテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンとの併用は、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがあるため、禁忌である。

HMG-CoA 還元酵素阻害剤のシンバスタチン、ロバスタチン及びアトルバスタチンとの併用は禁忌である。

警告及び使用上の注意

1)　過敏症

ポサコナゾールと他のアゾール系抗真菌薬との交差過敏症に関する情報はない。他のアゾール系抗真菌薬に対し過敏症のある患者にポサコナゾールを処方する場合は注意すること。

2)　肝毒性

ポサコナゾール投与中に肝機能障害（例：ALT、AST、ALP 及び総ビリルビンの軽度から中等度の増加、肝炎）が報告されている。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もいた。死亡に至る、より重症の肝機能障害の報告はまれである。

肝機能障害を有する患者ではポサコナゾールの血漿中濃度が増加する可能性があり、またこれらの患者での臨床経験は少ないため、肝機能障害を有する患者にポサコナゾールを投与する際は注意すること。

3)　肝機能のモニタリング

ポサコナゾールによる治療開始前及び治療中は、肝機能検査を実施すること。ポサコナゾールによる治療中に肝機能検査値の上昇を発現した患者では、より重度の肝損傷の発現について定期的に観察すること。患者の管理には、肝機能の臨床評価（特に肝機能検査及びビリルビン）を含めること。肝疾患に一致する臨床徴候や症状が現れた場合、ポサコナゾールの中止を考慮すること。

4)　QTc 延長

一部のアゾール系抗真菌薬は、QT 延長を引き起こすことが知られている。QTc 間隔を延長することが知られ、CYP3A4の基質となる薬剤とポサコナゾールを併用しないこと。ポサコナ

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ゾールは以下のような不整脈を引き起こしやすい状態の患者には注意して投与すること：

- 先天的又は後天的 QTc 延長
- 心筋症、特に心不全を合併するもの
- 洞性徐脈
- 既存の不整脈の症状
- QTc 間隔を延長することが知られる薬剤との併用（**禁忌**の項で示された薬剤以外）

ポサコナゾールによる治療開始前及び治療中は、電解質障害、特にカリウム、マグネシウム又はカルシウムの血中濃度の変動を含む状態をモニタリングし、必要に応じて適正化すること。

5)　薬物相互作用

ポサコナゾールは CYP3A4を介する薬物代謝を阻害するため、CYP3A4により代謝される薬剤の使用中は、特定の状況下のみで使用すること。

6)　ミダゾラムなどのベンゾジアゼピン系薬剤

CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）の鎮静の延長や呼吸抑制のリスクが増大するおそれがあるため、明確に必要性があるときのみポサコナゾールを併用すること。CYP3A4により代謝されるベンゾジアゼピン系薬剤の用量調整を考慮すること。

7)　ビンクリスチンの毒性

ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

8)　リファマイシン系抗菌剤（リファンピシン、リファブチン）、抗けいれん剤（フェニトイン、カルバマゼピン、フェノバルビタール、プリミドン）、エファビレンツ及びシメチジン

これらの薬剤は併用によりポサコナゾールの血漿中濃度を著しく低下させるため、治療上の有益性が危険性を上回る場合を除き、これらの薬剤とポサコナゾールの併用は避けること。

9)　消化管機能障害

重度の消化管機能障害（例：重度の下痢）を有する患者での薬物動態データは限られている。重度の下痢や嘔吐のある患者は、ブレイクスルー真菌感染の有無を注意深く観察すること。

10)　添加剤

本剤は、懸濁液5 mL 中に約1.75 g のブドウ糖を添加剤として含む。グルコース・ガラクトー

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ス吸収不良症の患者には本剤を投与すべきでない。

薬物相互作用

1)　他剤のポサコナゾールへの影響

ポサコナゾールは *in vitro* でウリジン5'-二リン酸-グルクロン酸転移酵素（第Ⅱ相代謝酵素）により代謝され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程の阻害剤（例：ベラパミル、シクロスポリン、キニジン、クラリスロマイシン、エリスロマイシン）又は誘導剤（例：リファンピシン、リファブチン、抗けいれん剤）により、ポサコナゾールの血漿中濃度が前者では増加、後者では減少する可能性がある。

(1)　リファブチン

リファブチン（300 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC がそれぞれ57%及び51%低下した。治療上の有益性が危険性を上回る場合を除き、リファブチン及び類似の誘導剤（例：リファンピシン）とポサコナゾールの併用は避けること。

(2)　エファビレンツ

エファビレンツ（400 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ45%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、エファビレンツとポサコナゾールの併用は避けること。

(3)　ホスアンプレナビル

ホスアンプレナビルとポサコナゾールとの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ポサコナゾールとの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。ホスアンプレナビルの反復投与（700 mg 1日2回10日間）により、ポサコナゾール経口懸濁液（初日に200 mg を1回、2日目に200 mg を2回、以降400 mg を1日2回8日間）の C_{max} 及び AUC は、それぞれ21%及び23%低下した。ホスアンプレナビルとリトナビル併用時のホスアンプレナビル値に対するポサコナゾールの影響は不明である。

(4)　フェニトイン

フェニトイン（200 mg 1日1回）とポサコナゾールとの併用により、ポサコナゾールの C_{max} 及び AUC は、それぞれ41%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、フェニトイン及び類似の誘導剤（例：カルバマゼピン、フェノバルビタール、プリミドン）とポサコナゾールの併用は避けること。

(5)　H_2受容体拮抗薬及びプロトンポンプ阻害薬

シメチジン（400 mg 1日2回）とポサコナゾールとの併用によりポサコナゾールの吸収が

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低下し、ポサコナゾールの C_{max} 及び AUC がいずれも39%低下した。吸収の低下はおそらく胃酸産生の低下による。ポサコナゾールと H_2受容体拮抗薬との併用は、可能であれば避けること。

同様に、エソメプラゾール（40 mg/日）とポサコナゾール400 mg を併用した際のポサコナゾールの平均 C_{max} 及び AUC は、ポサコナゾール400 mg を単剤投与したときと比べてそれぞれ46%及び32%低下した。ポサコナゾールとプロトンポンプ阻害薬の併用は、可能であれば避けること。

(6) 食事

ポサコナゾールの吸収は、食事によって明らかに増加する。

2) ポサコナゾールの他剤への影響

ポサコナゾールは CYP3A4の強力な阻害薬である。ポサコナゾールとタクロリムス、シロリムス、アタザナビル及びミダゾラムなどの CYP3A4の基質となる薬剤の併用は、CYP3A4基質の曝露量が大幅に高くなる可能性がある。ポサコナゾールと CYP3A4基質薬剤を併用して静注するときは十分に注意し、必要に応じて CYP3A4基質薬剤の用量を減量する。ポサコナゾールと CYP3A4基質薬剤を併用して経口投与するときは、血漿中濃度の増加により許容できない副作用が発現する可能性があるため、CYP3A4基質薬剤の血漿中濃度や副作用を注意深くモニタリングし、必要に応じて用量を調整する。健康被験者を対象とした複数の相互作用試験では、同量を投与された患者と比較してポサコナゾールの曝露量が高かった。ポサコナゾールの CYP3A4基質薬剤への影響は、健康被験者よりも患者で若干低い可能性があり、また患者でのポサコナゾールの曝露量にばらつきがあるため、患者間で差があると予測される。ポサコナゾールの曝露量は食事によって大きく影響を受けるため、ポサコナゾールの併用が CYP3A4基質薬剤の血漿中濃度に及ぼす影響は、食事を厳密に規定した方法で摂取しない限り患者内でも差がある可能性がある。

(1) テルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジン（CYP3A4基質）

ポサコナゾールとテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンの併用は禁忌である。併用により、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがある。

(2) 麦角アルカロイド

ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こすことがある。ポサコナゾールと麦角アルカロイドの併用は禁忌である。

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(3) CYP3A4により代謝されるHMG-CoA還元酵素阻害剤（例：シンバスタチン、ロバスタチン及びアトルバスタチン）

ポサコナゾールはCYP3A4により代謝されるHMG-CoA還元酵素阻害剤の血漿中濃度を大きく増加させることがある。血漿中濃度の増加により横紋筋融解症に至ることがあるため、ポサコナゾール投与中はHMG-CoA還元酵素阻害剤の投与を中止すべきである。

(4) ビンカアルカロイド

ビンカアルカロイドの大半（例：ビンクリスチン、ビンブラスチン）はCYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な有害事象を引き起こすおそれがあることが知られている。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。このため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

(5) リファブチン

ポサコナゾールとの併用により、リファブチンの C_{max} 及び AUC は、それぞれ31%及び72%増加した。治療上の有益性が危険性を上回る場合を除き、リファブチンとポサコナゾールの併用は避けること（リファブチンがポサコナゾールの血漿中濃度に及ぼす影響につき**薬物相互作用**の項も参照すること）。リファブチンとポサコナゾールを併用する場合は、全血球数及びリファブチンの血中濃度の増加に起因する副作用（例：ぶどう膜炎）を注意深くモニタリングすることを推奨する。

(6) シロリムス

健康被験者にポサコナゾール経口懸濁液400 mgを1日2回16日間反復経口投与した際、シロリムス（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で6.7倍及び8.9倍（範囲：3.1～17.5倍）に増加した。ポサコナゾールのシロリムスへの影響は患者では確認されていないが、患者でのポサコナゾールの曝露量にばらつきがあるため患者間で差があると考えられる。ポサコナゾールとシロリムスの併用は推奨されず、できる限り避けること。ポサコナゾールによる治療を開始する際は、シロリムスの用量を大幅に減量し、シロリムスの全血中トラフ濃度を頻回にモニタリングすることを推奨する。ポサコナゾールによる治療を開始する際、併用期間中及び中止する際は、シロリムスの血中濃度を測定し、必要に応じてシロリムスの用量を調整すること。ポサコナゾールとの併用中はシロリムスのトラフ濃度と AUC の変化に留意すること。通常の投与ではシロリムスの治療域範囲のトラフ濃度でも、ポサコナゾールとの併用中は治療域を下回る可能性がある。このため、通常の投与では治療域の上限とされる血中濃度をトラフ濃度として設定すべきである。また、臨床徴候や症状、臨床検査値及び組織生検結果に十分注意をすること。

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(7) シクロスポリン

シクロスポリンを安定した用量で処方されていた心臓移植患者にポサコナゾール経口懸濁液200 mg を1日1回投与した際、減量を必要とするシクロスポリンの血中濃度の増加がみられた。シクロスポリンの血中濃度の増加により腎毒性及び1例の白質脳症による死亡例を含む重篤な有害事象が臨床試験において報告されている。既にシクロスポリンを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シクロスポリンの用量を減量すべきである（例：現行用量の約3/4）。その後も、ポサコナゾールの併用期間中及び中止する際は、シクロスポリンの血中濃度を注意深くモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

(8) タクロリムス

ポサコナゾールとの併用によりタクロリムス（0.05 mg/kg 単回投与）の C_{max} 及び AUC は、それぞれ121%及び358%増加した。入院やポサコナゾールの投与中止に至った臨床的に意義のある相互作用が臨床試験において報告されている。既にタクロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、タクロリムスの用量を減量すべきである（例：現行用量の約1/3）。その後も、ポサコナゾールの併用期間中及び中止する際は、タクロリムスの血中濃度を注意深くモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(9) HIV プロテアーゼ阻害剤

HIV プロテアーゼ阻害剤は CYP3A4の基質であるため、ポサコナゾールとの併用によりこれらの HIV プロテアーゼ阻害剤の血漿中濃度が増加することが予測される。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル（300 mg 1日1回）と7日間併用投与した際のアタザナビルの C_{max} 及び AUC は、それぞれ平均で2.6倍及び3.7倍（範囲：1.2～26倍）に増加した。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル及びリトナビル（300 mg 1日1回及び100 mg 1日1回）と7日間併用投与した際のアタザナビルの C_{max} 及び AUC は、それぞれ平均で1.5倍及び2.5倍（範囲：0.9倍～4.1倍）に増加した。アタザナビル又はアタザナビルとリトナビルの併用治療にポサコナゾールを追加することにより、ビリルビンの血漿中濃度に増加がみられた。ポサコナゾールの併用期間中は、CYP3A4の基質である HIV プロテアーゼ阻害剤に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。

(10) CYP3A4により代謝されるミダゾラムなどのベンゾジアゼピン系薬剤

健康被験者での試験で、ポサコナゾール経口懸濁液（200 mg 1日1回10日間）との併用により、ミダゾラム静注時（0.05 mg/kg）の曝露量（AUC）が83%増加した。健康被験者での他の試験では、ポサコナゾール経口懸濁液の反復投与（200 mg 1日2回7日間）との併用により、ミダゾラム静注時（0.4 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で1.3倍及

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び4.6倍（範囲：1.7倍～6.4倍）に増加した。ポサコナゾール経口懸濁液400 mg 1日2回7日間との併用投与では、ミダゾラム静注時の C_{max} 及び AUC は、それぞれ1.6倍及び6.2倍（範囲：1.6倍～7.6倍）に増加した。両投与量のポサコナゾールとの併用により、ミダゾラム経口投与時（2 mg 単回投与）の C_{max} 及び AUC がそれぞれ2.2倍及び4.5倍に増加した。さらに、ポサコナゾール経口懸濁液（200 mg 又は400 mg）により、ポサコナゾールの併用期間中にミダゾラムの終末相 $t_{1/2}$ の平均が約3～4時間から8～10時間に延長した。

鎮静が延長するおそれがあるため、CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）とポサコナゾールを併用する際は、用量調整を考慮すること。

(11) CYP3A により代謝されるカルシウムチャネル遮断薬（例：ジルチアゼム、ベラパミル、ニフェジピン、ニソルジピン）

ポサコナゾールの併用期間中、カルシウムチャネル遮断薬に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を調整すること。

(12) ジゴキシン

他のアゾール系抗真菌薬ではジゴキシンの血中濃度増加との関連が知られている。したがって、ポサコナゾールはジゴキシンの血漿中濃度を増加させる可能性があり、ポサコナゾールでの治療開始時又は投与中止時には、ジゴキシンの血中濃度をモニタリングすること。

(13) スルホニル尿素剤

健康被験者において glipizide とポサコナゾールを併用した際に、グルコースの血中濃度が低下した被験者が認められた。糖尿病患者ではグルコースの血中濃度をモニタリングすることを推奨する。

3)　小児

薬物相互作用試験は成人でのみ実施された。

妊婦及び授乳婦

1)　妊婦

妊婦でのポサコナゾールの使用情報は十分ではない。動物試験では生殖毒性が認められている。ヒトに対する潜在的なリスクは不明である。

妊娠する可能性のある女性は、治療中は有効な避妊法を使用すること。妊娠中のポサコナゾールの使用は、母親への治療上の有益性が胎児への危険性を明らかに上回る場合のみとすること。

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2)　授乳婦

ポサコナゾールは授乳中のラットにおいて乳汁中に排出されている。ヒト乳汁中へのポサコナゾールの移行は検討していない。ポサコナゾール治療開始時に授乳を中止すること。

3)　生殖能

ポサコナゾールを最高180 mg/kg（健康被験者で400 mg を1日2回投与した際の定常状態である血漿中濃度の1.7倍に相当）投与した雄ラット、及び最高45 mg/kg（同2.2倍に相当）投与した雌ラットの生殖能にポサコナゾールの影響は認められなかった。ポサコナゾールの生殖能への影響を評価したヒトでの臨床経験はない。

運転及び機械作業への影響

運転及び機械作業に影響を及ぼす可能性がある有害事象（例：浮動性めまい、傾眠）がポサコナゾールの使用と関連して報告されているため、注意が必要である。

副作用

1)　安全性の概要

ポサコナゾール経口懸濁液の安全性は、臨床試験に組み入れられた2,400例を超える患者及び健康被験者、並びに市販後経験を元に評価された。発現割合が高かった重篤な副作用は、悪心、嘔吐、下痢、発熱及びビリルビン増加であった。

ポサコナゾール腸溶錠の安全性は、臨床試験に組み入れられた336例の患者及び健康被験者を元に評価された。ポサコナゾール腸溶錠の安全性プロファイルは、ポサコナゾール経口懸濁液と類似していた。

2)　有害事象の集計表

器官別大分類別の有害事象を発現割合別［非常によくみられる（≥1/10）、よくみられる（≥1/100～<1/10）、あまりみられない（≥1/1,000～<1/100）、まれな（≥1/10,000～<1/1,000）、非常にまれな（<1/10,000）、不明］に[表 1.6-14]に示す。

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表 1.6-14　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）

血液およびリンパ系障害 よくみられる： あまりみられない： まれな：	 好中球減少症 血小板減少症、白血球減少症、貧血、好酸球増加症、リンパ節症、脾臓梗塞 溶血性尿毒症症候群、血栓性血小板減少性紫斑病、汎血球減少症、凝血異常、出血
免疫系障害 あまりみられない： まれな：	 アレルギー反応 過敏症反応
内分泌障害 まれな：	 副腎機能不全、血中ゴナドトロピン減少
代謝および栄養障害 よくみられる： あまりみられない：	 電解質失調、食欲不振、食欲減退、低カリウム血症、低マグネシウム血症 高血糖、低血糖症
精神障害 あまりみられない： まれな：	 異常な夢、錯乱状態、睡眠障害 精神病性障害、うつ病
神経系障害 よくみられる： あまりみられない： まれな：	 錯感覚、浮動性めまい、傾眠、頭痛、味覚異常 痙攣、ニューロパチー、感覚鈍麻、振戦、失語症、不眠症 脳血管発作、脳症、末梢性ニューロパチー、失神
眼障害 あまりみられない： まれな：	 霧視、羞明、視力低下 複視、暗点
耳および迷路障害 まれな：	 聴覚障害
心臓障害 あまりみられない： まれな：	 QT 延長症候群‡、心電図異常‡、動悸、徐脈、上室性期外収縮、頻脈 トルサード ド ポアント、突然死、心室性頻脈、心肺停止、心不全、心筋梗塞
血管障害 よくみられる： あまりみられない： まれな：	 高血圧 低血圧、血管炎 肺塞栓症、深部静脈血栓症
呼吸器、胸郭および縦隔障害 あまりみられない： まれな：	 咳嗽、鼻出血、しゃっくり、鼻閉、胸膜痛、頻呼吸 肺高血圧症、間質性肺炎、肺臓炎
胃腸障害 非常によくみられる： よくみられる： あまりみられない： まれな：	 悪心 嘔吐、腹痛、下痢、消化不良、口内乾燥、鼓腸、便秘、肛門直腸不快感 膵炎、腹部膨満、小腸炎、心窩部不快感、おくび、胃食道逆流性疾患、口腔浮腫 胃腸出血、イレウス
肝胆道系障害 よくみられる： あまりみられない： まれな：	 肝機能検査（ALT、AST、ビリルビン、ALP、GGT 増加）上昇 肝細胞損傷、肝炎、黄疸、肝腫大、胆汁うっ滞、肝毒性、肝機能異常 肝不全、胆汁うっ滞性肝炎、肝脾腫大、肝圧痛、固定姿勢保持困難
皮膚および皮下組織障害 よくみられる： あまりみられない： まれな：	 発疹、そう痒症 口腔内潰瘍形成、脱毛症、皮膚炎、紅斑、点状出血 スティーヴンス・ジョンソン症候群、小水疱性皮疹
筋骨格系および結合組織障害 あまりみられない：	 背部痛、頚部痛、筋骨格痛、四肢痛
腎および尿路障害 あまりみられない： まれな：	 急性腎不全、腎不全、血中クレアチニン増加 腎尿細管性アシドーシス、間質性腎炎
生殖系および乳房障害 あまりみられない： まれな：	 月経障害 乳房痛

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表 1.6-14　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）（続き）

生殖系および乳房障害 あまりみられない： まれな：	 月経障害 乳房痛
一般・全身障害および投与部位の状態 よくみられる： あまりみられない： まれな：	 発熱、無力症、疲労 浮腫、疼痛、悪寒、倦怠感、胸部不快感、薬物不耐性、びくびく感、粘膜の炎症 舌浮腫、顔面浮腫
臨床検査 あまりみられない：	 薬物濃度変化、血中リン減少、胸部 X 線異常

† 経口懸濁液、腸溶錠、静注用濃厚溶液でみられた有害事象に基づく
‡ **警告及び使用上の注意**の項参照
ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALP：アルカリホスファターゼ、GGT：γ-グルタミルトランスフェラーゼ

3)　特定の副作用の記述

(1)　肝胆道系障害

ポサコナゾール経口懸濁液の市販後調査において死亡に至った重度の肝損傷が報告されている。

4)　副作用の報告

医薬品の有益性及び危険性のバランスを継続的に監視するため、製造販売後にも本剤と因果関係が疑われる有害事象（副作用）を報告することは重要である。医療従事者は国の有害事象報告システムを通じてそのような副作用を報告すること。

過量投与

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された患者で発現した有害事象は、より低用量で認められたものと同様であった。

また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

ポサコナゾールは血液透析で除去されない。ポサコナゾールの過量投与時に有効な特別な治療はなく、支持療法を考慮すること。

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1.6.2.1.2.2　　腸溶錠

販売名

Noxafil 100 mg 腸溶錠

剤形・含量

1錠中に100 mg のポサコナゾールを含有する腸溶錠
コーティングされた黄色の長さ17.5 mm のカプセル形、片側に100と刻印されている

効能・効果

ポサコナゾール腸溶錠には、成人における以下の真菌症の治療の適応がある：

1) アムホテリシン B 及びイトラコナゾールが無効又は不耐容の患者における侵襲性アスペルギルス症
2) アムホテリシン B が無効又は不耐容の患者におけるフサリウム症
3) イトラコナゾールが無効又は不耐容の患者におけるクロモブラストミコーシス及び菌腫
4) アムホテリシン B、イトラコナゾール及びフルコナゾールが無効又は不耐容の患者におけるコクシジオイデス症

無効とは、効果がある抗真菌薬を治療用量で最短7日間投与後、感染進行したこと又は改善がみられないことと定義する。

ポサコナゾール腸溶錠には、以下の患者における侵襲性真菌症の予防の適応もある：

1) 寛解導入化学療法施行中の急性骨髄性白血病（AML）又は骨髄異形成症候群（MDS）患者で、好中球減少症が遷延することが予測され、侵襲性真菌症を発症するリスクが高い患者
2) 移植片対宿主病に対し高用量免疫抑制療法を行う造血幹細胞移植（HSCT）患者で、侵襲性真菌症を発症するリスクが高い患者

口腔咽頭カンジダ症に使用する際は、ポサコナゾール経口懸濁液の添付文書（原文[1.6.2.2.2.1項]）を参照すること。

用法・用量

ポサコナゾール腸溶錠とポサコナゾール経口懸濁液に互換性はない。

ポサコナゾール腸溶錠と経口懸濁液では、投与頻度、服薬時の食事摂取の条件及び得られる血漿中濃度に違いがあるため、各剤形を置き換えて使用してはならない。したがって、各剤形の用法・用量に従うこと。

ポサコナゾールでの治療は、真菌症管理の経験、又はポサコナゾールが予防投与の適応とする

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疾患のリスクが高い患者での支持療法の経験がある医師によって開始されるべきである。

1)　用量

ポサコナゾールには、他に40 mg/mL 経口懸濁液及び300 mg 静注用濃厚溶液がある。ポサコナゾール腸溶錠は、ポサコナゾール経口懸濁液よりも概して高い血漿中濃度を示し、最適な血漿中濃度のために好ましい剤形である。

適応症による推奨用量を[表 1.6-15]に示す。

表 1.6-15　　適応症による推奨用量（原文 Table 1）

適応症	用法・用量
難治性侵襲性真菌症（IFI）／一次療法に不耐容の IFI の治療	初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用する。食事に関係なく投与可能である。 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。
侵襲性真菌症の予防	初日に300 mg（100 mg 錠3錠）を1日2回、その後は300 mg（100 mg 錠3錠）を1日1回服用する。食事に関係なく投与可能である。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。 AML 又は MDS 群患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する。

2)　特殊集団への投与

(1)　腎機能障害を有する患者への投与

ポサコナゾールの薬物動態に及ぼす腎機能障害の影響は認められず、用量調整は必要としない。

(2)　肝機能障害を有する患者への投与

ポサコナゾールの薬物動態に及ぼす肝機能障害（慢性肝疾患の Child-Pugh クラス C を含む）の影響についての限られたデータからは、正常な肝機能を有する被験者と比較して血漿中濃度が高かったが、用量調整の必要性を示唆するものではなかった。血漿中濃度が増加する可能性があるため、注意喚起することを推奨する。

(3)　小児への投与

18歳未満の小児に対するポサコナゾールの安全性及び有効性は確立していない。現在得られている情報は薬理学の項†に示しているが、推奨用量は設定できない。

† [1.6.2.2.2.2項]の原文を参照すること。

小児に対するポサコナゾール腸溶錠のデータは得られていない。

3)　投与方法

経口用

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ポサコナゾール腸溶錠は食事に関係なく投与できる。錠剤は粉砕したり、かんだり、割ったりせずにそのままの形で水とともに飲み込む。

禁忌

本薬又は本剤の成分に対して過敏症のある患者には禁忌である。

麦角アルカロイドとの併用は禁忌である。

CYP3A4基質のテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンとの併用は、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがあり、禁忌である。

HMG-CoA 還元酵素阻害剤のシンバスタチン、ロバスタチン及びアトルバスタチンとの併用は禁忌である。

警告及び使用上の注意

1)　過敏症

ポサコナゾールと他のアゾール系抗真菌薬との交差過敏症に関する情報はない。他のアゾール系抗真菌薬に対し過敏症のある患者にポサコナゾールを処方する場合は注意すること。

2)　肝毒性

ポサコナゾール投与中に肝機能障害（例：ALT、AST、ALP 及び総ビリルビンの軽度から中等度の増加、肝炎）が報告されている。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もいた。死亡に至る、より重症の肝機能障害の報告はまれである。

肝機能障害を有する患者ではポサコナゾールの血漿中濃度が増加する可能性があり、またこれらの患者での臨床経験は少ないため、肝機能障害を有する患者にポサコナゾールを投与する際は注意すること。

3)　肝機能のモニタリング

ポサコナゾールによる治療開始前及び治療中は、肝機能検査を実施すること。ポサコナゾールによる治療中に肝機能検査値の上昇を発現した患者では、より重度の肝損傷の発現について定期的に観察すること。患者の管理には、肝機能の臨床評価（特に肝機能検査及びビリルビン）を含めること。肝疾患に一致する臨床徴候や症状が現れた場合、ポサコナゾールの中止を考慮すること。

4)　QTc 延長

一部のアゾール系抗真菌薬は、QT 延長を引き起こすことが知られている。QTc 間隔を延長することが知られ、CYP3A4の基質となる薬剤とポサコナゾールを併用しないこと。ポサコナゾールは以下のような不整脈を引き起こしやすい状態の患者には注意して投与すること：

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- 先天的又は後天的 QTc 延長
- 心筋症、特に心不全を合併するもの
- 洞性徐脈
- 既存の不整脈の症状
- QTc 間隔を延長することが知られる薬剤との併用（**禁忌**の項で示された薬剤以外）

ポサコナゾールによる治療開始前及び治療中は、電解質障害、特にカリウム、マグネシウム又はカルシウムの血中濃度の変動を含む状態をモニタリングし、必要に応じて適正化すること。

5)　薬物相互作用

ポサコナゾールは CYP3A4を介する薬物代謝を阻害するため、CYP3A4により代謝される薬剤の使用中は、特定の状況下のみで使用すること。

6)　ミダゾラムなどのベンゾジアゼピン系薬剤

CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）の鎮静の延長や呼吸抑制のリスクが増大するおそれがあるため、明確に必要性があるときのみポサコナゾールを併用すること。CYP3A4により代謝されるベンゾジアゼピン系薬剤の用量調整を考慮すること。

7)　ビンクリスチンの毒性

ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

8)　リファマイシン系抗菌剤（リファンピシン、リファブチン）、抗けいれん剤（フェニトイン、カルバマゼピン、フェノバルビタール、プリミドン）及びエファビレンツ

これらの薬剤は併用によりポサコナゾールの血漿中濃度を著しく低下させるため、治療上の有益性が危険性を上回る場合を除き、これらの薬剤とポサコナゾールの併用は避けること。

9)　血漿中の曝露

ポサコナゾール腸溶錠投与後のポサコナゾールの血漿中濃度は、ポサコナゾール経口懸濁液投与後の血漿中濃度よりも概して高い。一部の患者では、ポサコナゾール腸溶錠投与後のポサコナゾールの血漿中濃度は、経時的に増加するおそれがある。現時点では、ポサコナゾール腸溶錠における、より高い曝露量での安全性情報は限られている。

10)　消化管機能障害

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重度の消化管機能障害（例：重度の下痢）を有する患者での薬物動態データは限られている。重度の下痢や嘔吐のある患者は、ブレイクスルー真菌感染の有無を注意深く観察すること。

薬物相互作用

1)　他剤のポサコナゾールへの影響

ポサコナゾールは *in vitro* でウリジン5'-二リン酸-グルクロン酸転移酵素（第Ⅱ相代謝酵素）により代謝され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程の阻害剤（例：ベラパミル、シクロスポリン、キニジン、クラリスロマイシン、エリスロマイシン）又は誘導剤（例：リファンピシン、リファブチン、抗けいれん剤）により、ポサコナゾールの血漿中濃度が前者では増加、後者では減少する可能性がある。

(1)　リファブチン

リファブチン（300 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC がそれぞれ57%及び51%低下した。治療上の有益性が危険性を上回る場合を除き、リファブチン及び類似の誘導剤（例：リファンピシン）とポサコナゾールの併用は避けること。

(2)　エファビレンツ

エファビレンツ（400 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ45%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、エファビレンツとポサコナゾールの併用は避けること。

(3)　ホスアンプレナビル

ホスアンプレナビルとポサコナゾールとの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ポサコナゾールとの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。ホスアンプレナビルの反復投与（700 mg 1日2回10日間）により、ポサコナゾール経口懸濁液（初日に200 mg を1回、2日目に200 mg を2回、以降400 mg を1日2回8日間）の C_{max} 及び AUC は、それぞれ21%及び23%低下した。ホスアンプレナビルとリトナビル併用時のホスアンプレナビル値に対するポサコナゾールの影響は不明である。

(4)　フェニトイン

フェニトイン（200 mg 1日1回）とポサコナゾールとの併用により、ポサコナゾールの C_{max} 及び AUC は、それぞれ41%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、フェニトイン及び類似の誘導剤（例：カルバマゼピン、フェノバルビタール、プリミドン）とポサコナゾールの併用は避けること。

(5)　H_2受容体拮抗薬及びプロトンポンプ阻害薬

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制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬とポサコナゾール腸溶錠との併用による、臨床的に関連がある影響はみられていない。制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬とポサコナゾール腸溶錠を併用するときは、ポサコナゾール腸溶錠の用量調整は必要ない。

2)　ポサコナゾールの他剤への影響

ポサコナゾールは CYP3A4の強力な阻害薬である。ポサコナゾールとタクロリムス、シロリムス、アタザナビル及びミダゾラムなどの CYP3A4の基質となる薬剤の併用は、CYP3A4基質の曝露量が大幅に高くなる可能性がある。ポサコナゾールと CYP3A4基質薬剤を併用して静注するときは十分に注意し、必要に応じて CYP3A4基質薬剤の用量を減量する。ポサコナゾールと CYP3A4基質薬剤を併用して経口投与するときは、血漿中濃度の増加により許容できない副作用が発現する可能性があるため、CYP3A4基質薬剤の血漿中濃度や副作用を注意深くモニタリングし、必要に応じて用量を調整する。健康被験者を対象とした複数の相互作用試験では、同量を投与された患者と比較してポサコナゾールの曝露量が高かった。ポサコナゾールの CYP3A4基質薬剤への影響は、健康被験者よりも患者で若干低い可能性があり、また患者でのポサコナゾールの曝露量にばらつきがあるため、患者間で差があると予測される。ポサコナゾールの併用が CYP3A4基質薬剤の血漿中濃度に及ぼす影響は、患者内でも差がある可能性がある。

(1)　テルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジン（CYP3A4基質）

ポサコナゾールとテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンの併用は禁忌である。併用により、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがある。

(2)　麦角アルカロイド

ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こすことがある。ポサコナゾールと麦角アルカロイドの併用は禁忌である。

(3)　CYP3A4により代謝される HMG-CoA 還元酵素阻害剤（例：シンバスタチン、ロバスタチン及びアトルバスタチン）

ポサコナゾールは CYP3A4により代謝される HMG-CoA 還元酵素阻害剤の血漿中濃度を大きく増加させることがある。血漿中濃度の増加により横紋筋融解症に至ることがあるため、ポサコナゾール投与中は HMG-CoA 還元酵素阻害剤の投与を中止すべきである。

(4)　ビンカアルカロイド

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ビンカアルカロイドの大半（例：ビンクリスチン、ビンブラスチン）は CYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な有害事象を引き起こすおそれがあることが知られている。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。このため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

(5) リファブチン

ポサコナゾールとの併用により、リファブチンの C_{max} 及び AUC は、それぞれ31%及び72%増加した。治療上の有益性が危険性を上回る場合を除き、リファブチンとポサコナゾールの併用は避けること（リファブチンがポサコナゾールの血漿中濃度に及ぼす影響につき、**薬物相互作用**の項も参照すること）。リファブチンとポサコナゾールを併用する場合は、全血球数及びリファブチンの血中濃度の増加に起因する副作用（例：ぶどう膜炎）を注意深くモニタリングすることを推奨する。

(6) シロリムス

健康被験者にポサコナゾール経口懸濁液400 mg を1日2回16日間反復経口投与した際、シロリムス（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で6.7倍及び8.9倍（範囲：3.1～17.5倍）に増加した。ポサコナゾールのシロリムスへの影響は患者では確認されていないが、患者でのポサコナゾールの曝露量にばらつきがあるため患者間で差があると考えられる。ポサコナゾールとシロリムスの併用は推奨されず、できる限り避けること。ポサコナゾールによる治療を開始する際は、シロリムスの用量を大幅に減量し、シロリムスの全血中トラフ濃度を頻回にモニタリングすることを推奨する。ポサコナゾールによる治療を開始する際、併用期間中及び中止する際は、シロリムスの血中濃度を測定し、必要に応じてシロリムスの用量を調整すること。ポサコナゾールとの併用中はシロリムスのトラフ濃度と AUC の変化に留意すること。通常の投与ではシロリムスの治療域範囲のトラフ濃度でも、ポサコナゾールとの併用中は治療域を下回る可能性がある。このため、通常の投与では治療域の上限とされる血中濃度をトラフ濃度として設定すべきである。また、臨床徴候や症状、臨床検査値及び組織生検結果に十分注意をすること。

(7) シクロスポリン

シクロスポリンを安定した用量で処方されていた心臓移植患者にポサコナゾール経口懸濁液200 mg を1日1回投与した際、減量を必要とするシクロスポリンの血中濃度の増加がみられた。シクロスポリンの血中濃度の増加により腎毒性及び1例の白質脳症による死亡例を含む重篤な有害事象が臨床試験において報告されている。既にシクロスポリンを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シクロスポリンの

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用量を減量すべきである（例：現行用量の約3/4）。その後も、ポサコナゾールの併用期間中及び中止する際は、シクロスポリンの血中濃度を注意深くモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

(8) タクロリムス

ポサコナゾールとの併用によりタクロリムス（0.05 mg/kg 単回投与）の C_{max} 及び AUC は、それぞれ121%及び358%増加した。入院やポサコナゾールの投与中止に至った臨床的に意義のある相互作用が臨床試験において報告されている。既にタクロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、タクロリムスの用量を減量すべきである（例：現行用量の約1/3）。その後も、ポサコナゾールの併用期間中及び中止する際は、タクロリムスの血中濃度を注意深くモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(9) HIV プロテアーゼ阻害剤

HIV プロテアーゼ阻害剤は CYP3A4の基質であるため、ポサコナゾールとの併用によりこれらの HIV プロテアーゼ阻害剤の血漿中濃度が増加することが予測される。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル（300 mg 1日1回）と7日間併用投与した際のアタザナビルの C_{max} 及び AUC は、それぞれ平均で2.6倍及び3.7倍（範囲：1.2～26倍）に増加した。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル及びリトナビル（300 mg 1日1回及び100 mg 1日1回）と7日間併用投与した際のアタザナビルの C_{max} 及び AUC は、それぞれ平均で1.5倍及び2.5倍（範囲：0.9倍～4.1倍）に増加した。アタザナビル又はアタザナビルとリトナビルの併用治療にポサコナゾールを追加することにより、ビリルビンの血漿中濃度に増加がみられた。ポサコナゾールの併用期間中は、CYP3A4の基質である HIV プロテアーゼ阻害剤に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。

(10) CYP3A4により代謝されるミダゾラムなどのベンゾジアゼピン系薬剤

健康被験者での試験で、ポサコナゾール経口懸濁液（200 mg 1日1回10日間）との併用により、ミダゾラム静注時（0.05 mg/kg）の曝露量（AUC）が83%増加した。健康被験者での他の試験では、ポサコナゾール経口懸濁液の反復投与（200 mg 1日2回7日間）との併用により、ミダゾラム静注時（0.4 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で1.3倍及び4.6倍（範囲：1.7倍～6.4倍）に増加した。ポサコナゾール経口懸濁液400 mg 1日2回7日間の併用投与では、ミダゾラム静注時の C_{max} 及び AUC は、それぞれ1.6倍及び6.2倍（範囲：1.6倍～7.6倍）に増加した。両投与量のポサコナゾールとの併用により、ミダゾラム経口投与時（2 mg 単回投与）の C_{max} 及び AUC がそれぞれ2.2倍及び4.5倍に増加した。さらに、ポサコナゾール経口懸濁液（200 mg 又は400 mg）により、ポサコナゾールの併用期間中にミダゾラムの終末相 $t_{1/2}$ の平均が約3～4時間から8～10時間に延長した。

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鎮静が延長するおそれがあるため、CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）とポサコナゾールを併用する際は、用量調整を考慮すること。

(11) CYP3A4により代謝されるカルシウムチャネル遮断薬（例：ジルチアゼム、ベラパミル、ニフェジピン、ニソルジピン）

ポサコナゾールの併用期間中、カルシウムチャネル遮断薬に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を調整すること。

(12) ジゴキシン

他のアゾール系抗真菌薬ではジゴキシンの血中濃度増加との関連が知られている。したがって、ポサコナゾールはジゴキシンの血漿中濃度を増加させる可能性があり、ポサコナゾールでの治療開始時又は投与中止時には、ジゴキシンの血中濃度をモニタリングすること。

(13) スルホニル尿素剤

健康被験者において glipizide とポサコナゾールを併用した際に、グルコースの血中濃度が低下した被験者が認められた。糖尿病患者ではグルコースの血中濃度のモニタリングを推奨する。

3)　小児

薬物相互作用試験は成人でのみ実施された。

妊婦及び授乳婦

1)　妊婦

妊婦でのポサコナゾールの使用情報は十分ではない。動物試験では生殖毒性が認められている。ヒトに対する潜在的なリスクは不明である。

妊娠する可能性のある女性は、治療中は有効な避妊法を使用すること。妊娠中のポサコナゾールの使用は、母親への治療上の有益性が胎児への危険性を明らかに上回る場合のみとすること。

2)　授乳婦

ポサコナゾールは授乳中のラットにおいて乳汁中に排出されている。ヒト乳汁中へのポサコナゾールの移行は検討していない。ポサコナゾール治療開始時に授乳を中止すること。

3)　生殖能

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ポサコナゾールを最高180 mg/kg（ヒトで300 mg 腸溶錠を投与した際の定常状態である血漿中濃度の3.4倍に相当）投与した雄ラット、及び最高45 mg/kg（同2.6倍に相当）投与した雌ラットの生殖能にポサコナゾールの影響は認められなかった。ポサコナゾールの生殖能への影響を評価したヒトでの臨床経験はない。

運転及び機械作業への影響

運転及び機械作業に影響を及ぼす可能性がある有害事象（例：浮動性めまい、傾眠）がポサコナゾールの使用と関連して報告されているため、注意が必要である。

副作用

安全性データは、主にポサコナゾール経口懸濁液の試験で得られたものである。

AML 及び MDS 患者並びに HSCT 後に移植片対宿主病（GVHD）が発症又は発症のリスクがある患者を対象にポサコナゾール腸溶錠の試験を実施した。錠剤での最長投与期間は、経口懸濁液よりも短かった。錠剤での血漿中濃度は経口懸濁液と比べて高かったため、有害事象の発現割合が高くなる可能性は否定できない。

1)　安全性の概要

(1)　ポサコナゾール腸溶錠

ポサコナゾール腸溶錠の安全性は主要な臨床試験に組み入れられた230例の患者で評価した。患者は真菌症予防を目的としたポサコナゾール腸溶錠の薬物動態及び安全性評価の非対照試験に組み入れられた。患者は、血液悪性腫瘍、化学療法後の好中球減少症、GVHD 及び HSCT 後などの基礎疾患を伴う免疫不全状態にあった。ポサコナゾール投与期間の中央値は28日間であった。20例が200 mg/日、210例が300 mg/日（各コホートとも初日は1日2回）を投与された。

(2)　ポサコナゾール腸溶錠と経口懸濁液の安全性

ポサコナゾール経口懸濁液の安全性は、臨床試験に組み入れられた2,400例を超える患者及び健康被験者、並びに市販後経験を元に評価された。発現割合が高かった重篤な副作用は、悪心、嘔吐、下痢、発熱及びビリルビン増加であった。

ポサコナゾール腸溶錠の安全性は、臨床試験に組み入れられた336例の患者及び健康被験者を元に評価された。ポサコナゾール腸溶錠の安全性プロファイルは、ポサコナゾール経口懸濁液と類似していた。

2)　有害事象の集計表

器官別大分類別の有害事象を発現割合別［非常によくみられる（≥1/10）、よくみられる（≥1/100～<1/10）、あまりみられない（≥1/1,000～<1/100）、まれな（≥1/10,000～<1/1,000）、非常にまれ

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な（<1/10,000）、不明］に[表 1.6-16]に示す。

表 1.6-16　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）

血液およびリンパ系障害 よくみられる： あまりみられない： まれな：	 好中球減少症 血小板減少症、白血球減少症、貧血、好酸球増加症、リンパ節症、脾臓梗塞 溶血性尿毒症症候群、血栓性血小板減少性紫斑病、汎血球減少症、凝血異常、出血
免疫系障害 あまりみられない： まれな：	 アレルギー反応 過敏症反応
内分泌障害 まれな：	 副腎機能不全、血中ゴナドトロピン減少
代謝および栄養障害 よくみられる： あまりみられない：	 電解質失調、食欲不振、食欲減退、低カリウム血症、低マグネシウム血症 高血糖、低血糖症
精神障害 あまりみられない： まれな：	 異常な夢、錯乱状態、睡眠障害 精神病性障害、うつ病
神経系障害 よくみられる： あまりみられない： まれな：	 錯感覚、浮動性めまい、傾眠、頭痛、味覚異常 痙攣、ニューロパシー、感覚鈍麻、振戦、失語症、不眠症 脳血管発作、脳症、末梢性ニューロパシー、失神
眼障害 あまりみられない： まれな：	 霧視、羞明、視力低下 複視、暗点
耳および迷路障害 まれな：	 聴覚障害
心臓障害 あまりみられない： まれな：	 QT 延長症候群‡、心電図異常‡、動悸、徐脈、上室性期外収縮、頻脈 トルサード ド ポアント、突然死、心室性頻脈、心肺停止、心不全、心筋梗塞
血管障害 よくみられる： あまりみられない： まれな：	 高血圧 低血圧、血管炎 肺塞栓症、深部静脈血栓症
呼吸器、胸郭および縦隔障害 あまりみられない： まれな：	 咳嗽、鼻出血、しゃっくり、鼻閉、胸膜痛、頻呼吸 肺高血圧症、間質性肺炎、肺臓炎
胃腸障害 非常によくみられる： よくみられる： あまりみられない： まれな：	 悪心 嘔吐、腹痛、下痢、消化不良、口内乾燥、鼓腸、便秘、肛門直腸不快感 膵炎、腹部膨満、小腸炎、心窩部不快感、おくび、胃食道逆流性疾患、口腔浮腫 胃腸出血、イレウス
肝胆道系障害 よくみられる： あまりみられない： まれな：	 肝機能検査（ALT、AST、ビリルビン、ALP、GGT 増加）上昇 肝細胞損傷、肝炎、黄疸、肝腫大、胆汁うっ滞、肝毒性、肝機能異常 肝不全、胆汁うっ滞性肝炎、肝脾腫大、肝圧痛、固定姿勢保持困難
皮膚および皮下組織障害 よくみられる： あまりみられない： まれな：	 発疹、そう痒症 口腔内潰瘍形成、脱毛症、皮膚炎、紅斑、点状出血 スティーヴンス・ジョンソン症候群、小水疱性皮疹
筋骨格系および結合組織障害 あまりみられない：	 背部痛、頚部痛、筋骨格痛、四肢痛

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表 1.6-16　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）（続き）

腎および尿路障害 あまりみられない： まれな：	 急性腎不全、腎不全、血中クレアチニン増加 腎尿細管性アシドーシス、間質性腎炎
生殖系および乳房障害 あまりみられない： まれな：	 月経障害 乳房痛
一般・全身障害および投与部位の状態 よくみられる： あまりみられない： まれな：	 発熱、無力症、疲労 浮腫、疼痛、悪寒、倦怠感、胸部不快感、薬物不耐性、びくびく感、粘膜の炎症 舌浮腫、顔面浮腫
臨床検査 あまりみられない：	 薬物濃度変化、血中リン減少、胸部 X 線異常

† 経口懸濁液、腸溶錠、静注用濃厚溶液でみられた有害事象に基づく
‡ **警告及び使用上の注意**の項参照
ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALP：アルカリホスファターゼ、GGT：γ-グルタミルトランスフェラーゼ

3)　特定の副作用の記述

(1)　肝胆道系障害

ポサコナゾール経口懸濁液の市販後調査において死亡に至った重度の肝損傷が報告されている。

4)　副作用の報告

医薬品の有益性及び危険性のバランスを継続的に監視するため、製造販売後にも本剤と因果関係が疑われる有害事象（副作用）を報告することは重要である。医療従事者は国の有害事象報告システムを通じてそのような副作用を報告すること。

過量投与

ポサコナゾール腸溶錠では過量投与の報告はない。

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された患者で発現した有害事象は、より低用量で認められたものと同様であった。

また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

ポサコナゾールは血液透析で除去されない。ポサコナゾールの過量投与時に有効な特別な治療はなく、支持療法を考慮すること。

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1.6.2.1.2.3　　静注用濃厚溶液

販売名

Noxafil 300 mg 静注用濃厚溶液

剤形・含量

各バイアル中に300 mg のポサコナゾールを含有する静注用濃厚溶液
静注用濃厚溶液1 mL 中に18 mg のポサコナゾールを含有する

各バイアル中に462 mg（20 mmol）のナトリウムを添加物として含む
無色から黄色の透明な水溶液

効能・効果

ポサコナゾール静注用濃厚溶液には、成人における以下の真菌症の治療の適応がある：

1) アムホテリシン B 及びイトラコナゾールが無効又は不耐容の患者における侵襲性アスペルギルス症
2) アムホテリシン B が無効又は不耐容の患者におけるフサリウム症
3) イトラコナゾールが無効又は不耐容の患者におけるクロモブラストミコーシス及び菌腫
4) アムホテリシン B、イトラコナゾール及びフルコナゾールが無効又は不耐容の患者におけるコクシジオイデス症

無効とは、効果がある抗真菌薬を治療用量で最短7日間投与後、感染進行したこと又は改善がみられないことと定義する。

ポサコナゾール静注用濃厚溶液には、以下の患者における侵襲性真菌症の予防の適応もある：

1) 寛解導入化学療法施行中の急性骨髄性白血病（AML）又は骨髄異形成症候群（MDS）患者で、好中球減少症が遷延することが予想され、侵襲性真菌症を発症するリスクが高い患者
2) 移植片対宿主病に対し高用量免疫抑制療法を行う造血幹細胞移植（HSCT）患者で、侵襲性真菌症を発症するリスクが高い患者

口腔咽頭カンジダ症に使用する際は、ポサコナゾール経口懸濁液の添付文書（原文[1.6.2.2.2.1項]）を参照すること。

用法・用量

ポサコナゾールでの治療は、真菌症管理の経験、又はポサコナゾールが予防投与の適応とする疾患のリスクが高い患者での支持療法の経験がある医師によって開始されるべきである。

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1)　用量

ポサコナゾールには、他に経口剤（100 mg 腸溶錠及び40 mg/mL 経口懸濁液）がある。患者の容態が経口投与可能となり次第、速やかに経口剤へ切り替えることを推奨する。

適応症による推奨用量を[表 1.6-17]に示す。

表 1.6-17　　適応症による推奨用量（原文 Table 1）

適応症	用法・用量
難治性侵襲性真菌症（IFI）／一次療法に不耐容の IFI の治療	初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与する。 投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。
侵襲性真菌症の予防	初日に300 mg を1日2回、その後は300 mg を1日1回静脈内投与する。 投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。 AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続する。

ポサコナゾールは、中心静脈カテーテル又は末梢穿刺中心静脈カテーテルを含む中心静脈ラインから、約90分間かけて緩徐に点滴静注すること。ポサコナゾール静注用濃厚溶液の急速静注は行わないこと。中心静脈カテーテルが利用できない場合は、末梢静脈カテーテルから単回投与してもよい。末梢静脈カテーテルから注入する場合は、約30分間かけて静注すること。

2)　特殊集団への投与

(1)　腎機能障害を有する患者への投与

中等度又は重度（クレアチニンクリアランス：<50 mL/min）の腎機能障害を有する患者では、基剤であるスルホブチルエーテル β-シクロデキストリンナトリウム（SBECD）が蓄積するおそれがある。これらの患者では、患者の有益性及び危険性を考慮してポサコナゾール静注用濃厚溶液の使用が正当化されない限り、ポサコナゾールの経口剤を投与すること。これらの患者では、血清クレアチニン値を慎重にモニタリングすること。

(2)　肝機能障害を有する患者への投与

ポサコナゾールの薬物動態に及ぼす肝機能障害（慢性肝疾患の Child-Pugh クラス C を含む）の影響についての限られたデータからは、正常な肝機能を有する被験者と比較して血漿中濃度が高かったが、用量調整の必要性を示唆するものではなかった。血漿中濃度が増加する可能性があるため、注意喚起することを推奨する。

(3)　小児への投与

18歳未満の小児に対するポサコナゾール静注用濃厚溶液の安全性及び有効性は確立していない。

小児に対するデータは得られていない。

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ポサコナゾール静注用濃厚溶液は、非臨床での安全性の問題があるため18歳未満の小児に使用してはならない。

3)　投与方法

ポサコナゾール静注用濃厚溶液は、投与前の希釈が必要である。ポサコナゾールは、中心静脈カテーテル又は末梢穿刺中心静脈カテーテルを含む中心静脈ラインから、約90分間かけて緩徐に点滴静注すること。

ポサコナゾール静注用濃厚溶液の急速静注は行わないこと。

中心静脈カテーテルが利用できない場合は、末梢静脈カテーテルから単回投与してもよい。末梢静脈カテーテルから注入する場合は、注射部位反応を減らすために約30分間かけて静注すること。

禁忌

本薬又は本剤の成分に対して過敏症のある患者には禁忌である。

麦角アルカロイドとの併用は禁忌である。

CYP3A4基質のテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンとの併用は、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがあり、禁忌である。

HMG-CoA 還元酵素阻害剤のシンバスタチン、ロバスタチン及びアトルバスタチンとの併用は禁忌である。

警告及び使用上の注意

1)　過敏症

ポサコナゾールと他のアゾール系抗真菌薬との交差過敏症に関する情報はない。他のアゾール系抗真菌薬に対し過敏症のある患者にポサコナゾールを処方する場合は注意すること。

2)　肝毒性

ポサコナゾール投与中に肝機能障害（例：ALT、AST、ALP 及び総ビリルビンの増加、肝炎）が報告されている。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もいた。死亡に至る、より重症の肝機能障害の報告はまれである。

肝機能障害を有する患者ではポサコナゾールの血漿中濃度が増加する可能性があり、またこれらの患者での臨床経験は少ないため、肝機能障害を有する患者にポサコナゾールを投与する際は注意すること。

3)　腎機能のモニタリング

曝露量に差が生じるため、重度の腎障害を有する患者はブレイクスルー真菌感染の有無を注

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意深く観察すること。

4)　肝機能のモニタリング

ポサコナゾールによる治療開始前及び治療中は、肝機能検査を実施すること。ポサコナゾールによる治療中に肝機能検査値の上昇を発現した患者では、より重度の肝損傷の発現について定期的に観察すること。患者の管理には、肝機能の臨床評価（特に肝機能検査及びビリルビン）を含めること。肝疾患に一致する臨床徴候や症状が現れた場合、ポサコナゾールの中止を考慮すること。

5)　QTc 延長

一部のアゾール系抗真菌薬は、QT 延長を引き起こすことが知られている。QTc 間隔を延長することが知られ、CYP3A4の基質となる薬剤とポサコナゾールを併用しないこと。ポサコナゾールは以下のような不整脈を引き起こしやすい状態の患者には注意して投与すること：

- 先天的又は後天的 QTc 延長
- 心筋症、特に心不全を合併するもの
- 洞性徐脈
- 既存の不整脈の症状
- QTc 間隔を延長することが知られる薬剤との併用（**禁忌**の項で示された薬剤以外）

ポサコナゾールによる治療開始前及び治療中は、電解質障害、特にカリウム、マグネシウム又はカルシウムの血中濃度の変動を含む状態をモニタリングし、必要に応じて適正化すること。

ポサコナゾール静注用濃厚溶液投与後の C_{max} は、経口懸濁液の投与後と比較して4倍に増加する。それによる QTc 間隔への影響は否定できない。またポサコナゾールを末梢静脈から注入する場合は、推奨投与時間が30分であることから C_{max} を更に増加させる可能性があり、特に注意が必要である。

6)　薬物相互作用

ポサコナゾールは CYP3A4を介する薬物代謝を阻害するため、CYP3A4により代謝される薬剤の使用中は、特定の状況下のみで使用すること。

7)　ミダゾラムなどのベンゾジアゼピン系薬剤

CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）の鎮静の延長や呼吸抑制のリスクが増大するおそれがあるため、明確に必要性があるときのみポサコナゾールを併用すること。CYP3A4により代謝されるベンゾジアゼピン系薬剤の用量調整を考慮すること。

8)　ビンクリスチンの毒性

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ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

9)　リファマイシン系抗菌剤（リファンピシン、リファブチン）、抗けいれん剤（フェニトイン、カルバマゼピン、フェノバルビタール、プリミドン）及びエファビレンツ

これらの薬剤は併用によりポサコナゾールの血漿中濃度を著しく低下させるため、治療上の有益性が危険性を上回る場合を除き、これらの薬剤とポサコナゾールの併用は避けること。

10)　血漿中濃度

ポサコナゾール静注用濃厚溶液投与後のポサコナゾールの血漿中濃度は、ポサコナゾール経口懸濁液投与後の血漿中濃度よりも概して高い。

一部の患者では、ポサコナゾール静注用濃厚溶液投与後のポサコナゾールの血漿中濃度は、経時的に増加するおそれがある。現時点では、ポサコナゾール静注用濃厚溶液における、より高い曝露量での安全性情報は限られている。

11)　血栓塞栓症

ポサコナゾール静注用濃厚溶液では、血栓塞栓症が潜在的なリスクとして確認されているが、臨床試験ではみられていない。血栓性静脈炎は臨床試験でみられた。血栓塞栓症のあらゆる徴候や症状に注意を払うべきである。

12)　ナトリウム含有

ポサコナゾールの各バイアル中に462 mg（20 mmol）のナトリウムを含む。ナトリウム制限食の患者では、これを考慮に入れること。

薬物相互作用

以下の情報はポサコナゾール経口懸濁液又は初期の錠剤のデータから得られたものである。ポサコナゾールの吸収に影響を及ぼすもの（胃内 pH 又は胃運動に影響を及ぼす薬剤）を除き、ポサコナゾール経口懸濁液で起こる薬物相互作用はポサコナゾール静注用濃厚溶液でも同様に起こると考えられる。

1)　他剤のポサコナゾールへの影響

ポサコナゾールは *in vitro* でウリジン5’-二リン酸-グルクロン酸転移酵素（第Ⅱ相代謝酵素）により代謝され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程の阻害剤（例：ベラパミル、シクロスポリン、キニジン、クラリスロマイシ

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ン、エリスロマイシン）又は誘導剤（例：リファンピシン、リファブチン、抗けいれん剤）により、ポサコナゾールの血漿中濃度が前者では増加、後者では減少する可能性がある。

(1) リファブチン

リファブチン（300 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC がそれぞれ57%及び51%低下した。治療上の有益性が危険性を上回る場合を除き、リファブチン及び類似の誘導剤（例：リファンピシン）とポサコナゾールの併用は避けること。

(2) エファビレンツ

エファビレンツ（400 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ45%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、エファビレンツとポサコナゾールの併用は避けること。

(3) ホスアンプレナビル

ホスアンプレナビルとポサコナゾールとの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ポサコナゾールとの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。ホスアンプレナビルの反復投与（700 mg 1日2回10日間）により、ポサコナゾール経口懸濁液（初日に200 mg を1回、2日目に200 mg を2回、以降400 mg を1日2回8日間）の C_{max} 及び AUC は、それぞれ21%及び23%低下した。ホスアンプレナビルとリトナビル併用時のホスアンプレナビル値に対するポサコナゾールの影響は不明である。

(4) フェニトイン

フェニトイン（200 mg 1日1回）とポサコナゾールとの併用により、ポサコナゾールの C_{max} 及び AUC は、それぞれ41%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、フェニトイン及び類似の誘導剤（例：カルバマゼピン、フェノバルビタール、プリミドン）とポサコナゾールの併用は避けること。

2)　ポサコナゾールの他剤への影響

ポサコナゾールは CYP3A4の強力な阻害薬である。ポサコナゾールとタクロリムス、シロリムス、アタザナビル及びミダゾラムなどの CYP3A4の基質となる薬剤の併用は、CYP3A4基質の曝露量が大幅に高くなる可能性がある。ポサコナゾールと CYP3A4基質薬剤を併用して静注するときは十分に注意し、必要に応じて CYP3A4基質薬剤の用量を減量する。ポサコナゾールと CYP3A4基質薬剤を併用して経口投与するときは、血漿中濃度の増加により許容できない副作用が発現する可能性があるため、CYP3A4基質薬剤の血漿中濃度や副作用を注意深くモニタリングし、必要に応じて用量を調整する。

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(1) テルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジン（CYP3A4基質）

ポサコナゾールとテルフェナジン、アステミゾール、シサプリド、ピモジド、halofantrine 又はキニジンの併用は禁忌である。併用により、これらの薬剤の血漿中濃度が増加し、QTc 延長、及びまれにトルサード ド ポアントを引き起こすことがある。

(2) 麦角アルカロイド

ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こすことがある。ポサコナゾールと麦角アルカロイドの併用は禁忌である。

(3) CYP3A4により代謝される HMG-CoA 還元酵素阻害剤（例：シンバスタチン、ロバスタチン及びアトルバスタチン）

ポサコナゾールは CYP3A4により代謝される HMG-CoA 還元酵素阻害剤の血漿中濃度を大きく増加させることがある。血漿中濃度の増加により横紋筋融解症に至ることがあるため、ポサコナゾール投与中は HMG-CoA 還元酵素阻害剤の投与を中止すべきである。

(4) ビンカアルカロイド

ビンカアルカロイドの大半（例：ビンクリスチン、ビンブラスチン）は CYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な有害事象を引き起こすおそれがあることが知られている。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。このため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

(5) リファブチン

ポサコナゾール経口剤との併用により、リファブチンの C_{max} 及び AUC は、それぞれ31%及び72%増加した。治療上の有益性が危険性を上回る場合を除き、リファブチンとポサコナゾールの併用は避けること。リファブチンとポサコナゾールを併用する場合は、全血球数及びリファブチンの血中濃度の増加に起因する副作用（例：ぶどう膜炎）を注意深くモニタリングすることを推奨する。

(6) シロリムス

健康被験者にポサコナゾール経口懸濁液400 mg を1日2回16日間反復経口投与した際、シロリムス（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で6.7倍及び8.9倍（範囲：3.1～17.5倍）に増加した。ポサコナゾールのシロリムスへの影響は患者では確認されてい

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ないが、患者でのポサコナゾールの曝露量にばらつきがあるため患者間で差があると考えられる。ポサコナゾールとシロリムスの併用は推奨されず、できる限り避けること。ポサコナゾールによる治療を開始する際は、シロリムスの用量を大幅に減量し、シロリムスの全血中トラフ濃度を頻回にモニタリングすることを推奨する。ポサコナゾールによる治療を開始する際、併用期間中及び中止する際は、シロリムスの血中濃度を測定し、必要に応じてシロリムスの用量を調整すること。ポサコナゾールとの併用中はシロリムスのトラフ濃度と AUC の変化に留意すること。通常の投与ではシロリムスの治療域範囲のトラフ濃度でも、ポサコナゾールとの併用中は治療域を下回る可能性がある。このため、通常の投与では治療域の上限とされる血中濃度をトラフ濃度として設定すべきである。また、臨床徴候や症状、臨床検査値及び組織生検結果に十分注意をすること。

(7) シクロスポリン

シクロスポリンを安定した用量で処方されていた心臓移植患者にポサコナゾール経口懸濁液200 mg を1日1回投与した際、減量を必要とするシクロスポリンの血中濃度の増加がみられた。シクロスポリンの血中濃度の増加により腎毒性及び1例の白質脳症による死亡例を含む重篤な有害事象が臨床試験において報告されている。既にシクロスポリンを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シクロスポリンの用量を減量すべきである（例：現行用量の約3/4）。その後も、ポサコナゾールの併用期間中及び中止する際は、シクロスポリンの血中濃度を注意深くモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

(8) タクロリムス

ポサコナゾールとの併用によりタクロリムス（0.05 mg/kg 単回投与）の C_{max} 及び AUC は、それぞれ121%及び358%増加した。入院やポサコナゾールの投与中止に至った臨床的に意義のある相互作用が臨床試験において報告されている。既にタクロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、タクロリムスの用量を減量すべきである（例：現行用量の約1/3）。その後も、ポサコナゾールの併用期間中及び中止する際は、タクロリムスの血中濃度を注意深くモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(9) HIV プロテアーゼ阻害剤

HIV プロテアーゼ阻害剤は CYP3A4の基質であるため、ポサコナゾールとの併用によりこれらの HIV プロテアーゼ阻害剤の血漿中濃度が増加することが予測される。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル（300 mg 1日1回）と7日間併用投与した際のアタザナビルの C_{max} 及び AUC は、それぞれ平均で2.6倍及び3.7倍（範囲：1.2～26倍）に増加した。健康被験者にポサコナゾール経口懸濁液（400 mg 1日2回）をアタザナビル及びリトナビル（300 mg 1日1回及び100 mg 1日1回）と7日間併用投与した際の

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アタザナビルの C_{max} 及び AUC は、それぞれ平均で1.5倍及び2.5倍（範囲：0.9倍～4.1倍）に増加した。アタザナビル又はアタザナビルとリトナビルの併用治療にポサコナゾールを追加することにより、ビリルビンの血漿中濃度に増加がみられた。ポサコナゾールの併用期間中は、CYP3A4の基質である HIV プロテアーゼ阻害剤に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。

(10) CYP3A4により代謝されるミダゾラムなどのベンゾジアゼピン系薬剤

健康被験者での試験で、ポサコナゾール経口懸濁液（200 mg 1日1回10日間）との併用により、ミダゾラム静注時（0.05 mg/kg）の曝露量（AUC）が83%増加した。健康被験者での他の試験では、ポサコナゾール経口懸濁液の反復投与（200 mg 1日2回7日間）との併用により、ミダゾラム静注時（0.4 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均で1.3倍及び4.6倍（範囲：1.7倍～6.4倍）に増加した。ポサコナゾール経口懸濁液400 mg 1日2回7日間の併用投与では、ミダゾラム静注時の C_{max} 及び AUC は、それぞれ1.6倍及び6.2倍（範囲：1.6倍～7.6倍）に増加した。両投与量のポサコナゾールとの併用により、ミダゾラム経口投与時（2 mg 単回投与）の C_{max} 及び AUC がそれぞれ2.2倍及び4.5倍に増加した。さらに、ポサコナゾール経口懸濁液（200 mg 又は400 mg）により、ポサコナゾールの併用期間中にミダゾラムの終末相 $t_{1/2}$ の平均が約3～4時間から8～10時間に延長した。

鎮静が延長するおそれがあるため、CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）とポサコナゾールを併用する際は、用量調整を考慮すること。

(11) CYP3A4により代謝されるカルシウムチャネル遮断薬（例：ジルチアゼム、ベラパミル、ニフェジピン、ニソルジピン）

ポサコナゾールの併用期間中、カルシウムチャネル遮断薬に関連する有害事象及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を調整すること。

(12) ジゴキシン

他のアゾール系抗真菌薬ではジゴキシンの血中濃度増加との関連が知られている。したがって、ポサコナゾールはジゴキシンの血漿中濃度を増加させる可能性があり、ポサコナゾールでの治療開始時又は投与中止時には、ジゴキシンの血中濃度をモニタリングすること。

(13) スルホニル尿素剤

健康被験者において glipizide とポサコナゾールを併用した際に、グルコースの血中濃度が低下した被験者が認められた。糖尿病患者ではグルコースの血中濃度のモニタリングを推奨する。

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3)　小児

薬物相互作用試験は成人でのみ実施された。

妊婦及び授乳婦

1)　妊婦

妊婦でのポサコナゾールの使用情報は十分ではない。動物試験では生殖毒性が認められている。ヒトに対する潜在的なリスクは不明である。

妊娠する可能性のある女性は、治療中は有効な避妊法を使用すること。妊娠中のポサコナゾールの使用は、母親への治療上の有益性が胎児への危険性を明らかに上回る場合のみとすること。

2)　授乳婦

ポサコナゾールは授乳中のラットにおいて乳汁中に排出されている。ヒト乳汁中へのポサコナゾールの移行は検討していない。ポサコナゾール治療開始時に授乳を中止すること。

3)　生殖能

ポサコナゾールを最高180 mg/kg（ヒトで300 mg 静注した際の血漿中濃度の2.8倍に相当）投与した雄ラット、及び最高45 mg/kg（同3.4倍に相当）投与した雌ラットの生殖能にポサコナゾールの影響は認められなかった。ポサコナゾールの生殖能への影響を評価したヒトでの臨床経験はない。

運転及び機械作業への影響

運転及び機械作業に影響を及ぼす可能性がある有害事象（例：浮動性めまい、傾眠）がポサコナゾールの使用と関連して報告されているため、注意が必要である。

副作用

安全性データは、主にポサコナゾール経口懸濁液の試験で得られたものである。

AML 及び MDS 患者並びに HSCT 後に GVHD が発症又は発症のリスクがある患者を対象にポサコナゾール静注用濃厚溶液の試験を実施した。静注用濃厚溶液での最長投与期間は、経口懸濁液よりも短かった。静注用濃厚溶液での血漿中濃度は経口懸濁液と比べて高かったため、有害事象の発現割合が高くなる可能性は否定できない。

1)　安全性の概要

(1)　ポサコナゾール静注用濃厚溶液の安全性

健康被験者を対象とした初期の試験では、末梢静脈カテーテルから30分間かけてポサコナゾールを単回注入した際の注入部位反応の発現割合は12%であった（血栓性静脈炎の発

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現割合は4%)。末梢静脈カテーテルからポサコナゾールを反復注入した際は、それに関連して血栓性静脈炎が発現した（発現割合：60%)。そのため、その後の試験ではポサコナゾールは中心静脈カテーテルから投与された。中心静脈カテーテルが使用できない場合は、30分間かけて末梢静脈カテーテルから単回投与してもよい。末梢静脈カテーテルからの注入が30分を超えると、注入部位反応及び血栓性静脈炎の発現割合が増加する。

臨床試験で患者268例を対象にポサコナゾール静注用濃厚溶液の安全性を評価した。患者は真菌症予防を目的としたポサコナゾール静注用濃厚溶液の薬物動態及び安全性評価の非対照試験に組み入れられた（P05520試験)。11例にポサコナゾール静注用濃厚溶液200 mgを単回投与、21例に200 mg/日を14日間（中央値)、237例に300 mg/日を9日間（中央値）投与した。28日間を超えて投与した際の安全性データは得られていない。高齢者に投与した際の安全性データは限定的である。

ポサコナゾール静注用濃厚溶液300 mg 1日1回の静注期間中に認められた有害事象で発現割合が最も高い（>25%）事象は、下痢（32%）であった。

ポサコナゾール静注用濃厚溶液300 mg 1日1回で投与中止に至った有害事象で発現割合が最も高い（>1%）事象は、AML（1%）であった。

2)　有害事象の集計表

器官別大分類別の有害事象を発現割合別[非常によくみられる(≥1/10)、よくみられる(≥1/100～<1/10)、あまりみられない（≥1/1,000～<1/100)、まれな（≥1/10,000～<1/1,000)、非常にまれな（<1/10,000)、不明］に[表 1.6-18]に示す。

表 1.6-18　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）

血液およびリンパ系障害 よくみられる： あまりみられない： まれな：	 好中球減少症 血小板減少症、白血球減少症、貧血、好酸球増加症、リンパ節症、脾臓梗塞 溶血性尿毒症症候群、血栓性血小板減少性紫斑病、汎血球減少症、凝血異常、出血
免疫系障害 あまりみられない： まれな：	 アレルギー反応 過敏症反応
内分泌障害 まれな：	 副腎機能不全、血中ゴナドトロピン減少
代謝および栄養障害 よくみられる： あまりみられない：	 電解質失調、食欲不振、食欲減退、低カリウム血症、低マグネシウム血症 高血糖、低血糖症
精神障害 あまりみられない： まれな：	 異常な夢、錯乱状態、睡眠障害 精神病性障害、うつ病
神経系障害 よくみられる： あまりみられない： まれな：	 錯感覚、浮動性めまい、傾眠、頭痛、味覚異常 痙攣、ニューロパチー、感覚鈍麻、振戦、失語症、不眠症 脳血管発作、脳症、末梢性ニューロパチー、失神

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表 1.6-18　　器官別大分類及び発現割合別の有害事象†（原文 Table 2）（続き）

眼障害 あまりみられない： まれな：	 霧視、羞明、視力低下 複視、暗点
耳および迷路障害 まれな：	 聴覚障害
心臓障害 あまりみられない： まれな：	 QT 延長症候群‡、心電図異常‡、動悸、徐脈、上室性期外収縮、頻脈 トルサード ド ポアント、突然死、心室性頻脈、心肺停止、心不全、心筋梗塞
血管障害 よくみられる： あまりみられない： まれな：	 高血圧 低血圧、血栓性静脈炎、血管炎 肺塞栓症、深部静脈血栓症
呼吸器、胸郭および縦隔障害 あまりみられない： まれな：	 咳嗽、鼻出血、しゃっくり、鼻閉、胸膜痛、頻呼吸 肺高血圧症、間質性肺炎、肺臓炎
胃腸障害 非常によくみられる： よくみられる： あまりみられない： まれな：	 悪心 嘔吐、腹痛、下痢、消化不良、口内乾燥、鼓腸、便秘、肛門直腸不快感 膵炎、腹部膨満、小腸炎、心窩部不快感、おくび、胃食道逆流性疾患、口腔浮腫 胃腸出血、イレウス
肝胆道系障害 よくみられる： あまりみられない： まれな：	 肝機能検査（ALT、AST、ビリルビン、ALP、GGT 増加）上昇 肝細胞損傷、肝炎、黄疸、肝腫大、胆汁うっ滞、肝毒性、肝機能異常 肝不全、胆汁うっ滞性肝炎、肝脾腫大、肝圧痛、固定姿勢保持困難
皮膚および皮下組織障害 よくみられる： あまりみられない： まれな：	 発疹、そう痒症 口腔内潰瘍形成、脱毛症、皮膚炎、紅斑、点状出血 スティーヴンス・ジョンソン症候群、小水疱性皮疹
筋骨格系および結合組織障害 あまりみられない：	 背部痛、頚部痛、筋骨格痛、四肢痛
腎および尿路障害 あまりみられない： まれな：	 急性腎不全、腎不全、血中クレアチニン増加 腎尿細管性アシドーシス、間質性腎炎
生殖系および乳房障害 あまりみられない： まれな：	 月経障害 乳房痛
一般・全身障害および投与部位の状態 よくみられる： あまりみられない： まれな：	 発熱、無力症、疲労 浮腫、疼痛、悪寒、倦怠感、胸部不快感、薬物不耐性、びくびく感、注入部位疼痛、注入部位静脈炎、注入部位血栓、粘膜の炎症 舌浮腫、顔面浮腫
臨床検査 あまりみられない：	 薬物濃度変化、血中リン減少、胸部 X 線異常

† 経口懸濁液、腸溶錠、静注用濃厚溶液でみられた有害事象に基づく
‡ **警告及び使用上の注意**の項参照
ALT：アラニンアミノトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALP：アルカリホスファターゼ、GGT：γ-グルタミルトランスフェラーゼ

3)　特定の副作用の記述

(1)　肝胆道系障害

市販後調査において死亡に至った重度の肝損傷が報告されている。

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4)　副作用の報告

医薬品の有益性及び危険性のバランスを継続的に監視するため、製造販売後にも本剤と因果関係が疑われる有害事象（副作用）を報告することは重要である。医療従事者は国の有害事象報告システムを通じてそのような副作用を報告すること。

過量投与

ポサコナゾール静注用濃厚溶液では過量投与の報告はない。

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された患者で発現した有害事象は、より低用量で認められたものと同様であった。

また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

ポサコナゾールは血液透析で除去されない。ポサコナゾールの過量投与時に有効な特別な治療はなく、支持療法を考慮すること。

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1.6.2.1.3　　オーストラリア添付文書の概要（和訳）

1.6.2.1.3.1　　徐放錠及び経口懸濁液

販売名

Noxafil® 100 mg 徐放錠
Noxafil® 40 mg/mL 経口懸濁液

剤形・含量

徐放錠は、1錠中に100 mg のポサコナゾールを含有する、コーティングされた黄色のカプセル形をした錠剤である。

経口懸濁液は、1 mL 中に40 mg のポサコナゾールを含有する、チェリー様のにおいを有する白色の即時放出型の経口懸濁液である。

外観及び貯蔵方法

ポサコナゾール経口懸濁液は、1 mL 中に40 mg のポサコナゾールを含む。ポサコナゾール経口懸濁液105 mL は、チャイルドレジスタントキャップを施した欧州薬局方準拠の褐色の123 mL Type IV ガラスボトルに充填されている。各ボトルには、透明のポリスチレン製で2.5 mL 又は5 mL の懸濁液を計量できる目盛り付き計量スプーンが付属している。使用前によく振盪すること。25°C 未満で保存すること。凍結させないこと。

ポサコナゾール徐放錠 100 mg は、コーティングされた黄色のカプセル形をした錠剤であり、片側に「100」と刻印されている。ポサコナゾール徐放錠は24錠及び96錠入りのブリスターパックとして販売している。

ポサコナゾール徐放錠は30°C 未満で保存すること。製品本来の容器に入れて保存すること。

効能・効果

ポサコナゾールには、13歳以上の患者における以下の侵襲性真菌症の治療の適応がある：

- 他の治療が不耐容又は無効な疾患を有する患者における侵襲性アスペルギルス症
- 他の治療が不耐容又は無効な疾患を有する患者におけるフサリウム症、ムーコル症、コクシジオイデス症、クロモブラストミコーシス及び菌腫

ポサコナゾールには、以下の適応もある：

- イトラコナゾール及びフルコナゾールが無効な疾患を有する患者を含む、免疫抑制状態の成人における口腔咽頭カンジダ症の治療
- 持続性好中球減少症患者又は造血幹細胞移植（HSCT）患者のような侵襲性真菌症を発症するリスクが高い13歳以上の患者における侵襲性真菌症の予防

口腔咽頭カンジダ症の治療を受ける患者に対しては、経口懸濁液のみを使用する。

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用法・用量

ポサコナゾール経口懸濁液は、一回分の食事とともに服用すること。一回分の食事ができない患者では、液体栄養補助剤とともに服用する。

ポサコナゾール徐放錠は、分割したり、砕いたり、かんだりせずに丸ごと飲み込むこと。ポサコナゾール徐放錠は食事の摂取に関係なく服用できる。

治療上の有益性が危険性を上回る場合を除き、ポサコナゾールの血漿中濃度を低下させる薬剤との併用は避けること。しかしながら、併用する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。

ポサコナゾール徐放錠及びポサコナゾール経口懸濁液に互換性はない。

処方医は各剤形に特有の投与に関する指示事項を守ること。ポサコナゾール徐放錠とポサコナゾール経口懸濁液では用法が異なるため、各剤形を置き換えて使用してはならない。各剤形に特有の推奨用量に従うこと。

1)　ポサコナゾール経口懸濁液の用法

使用前によく振盪すること。

(1)　難治性侵襲性真菌症／不耐容の侵襲性真菌症の治療

ポサコナゾールは400 mg（10 mL）を1日2回、食事又は240 mL の栄養補助剤とともに服用すること。投与をさらに1日4回200 mg（5 mL）に分割すると、特に経口摂取量が少ない患者でのポサコナゾールの曝露量が増加することが明らかになっている。1日用量を800 mg 超に増量した場合でも、ポサコナゾールの曝露量が更に増加することはない。

(2)　HIV 感染患者における口腔咽頭カンジダ症の治療

ポサコナゾールは初日に負荷用量として200 mg（5 mL）を1日1回、その後は100 mg（2.5 mL）を1日1回13日間服用すること。

HIV 感染患者におけるイトラコナゾール及びフルコナゾールが無効の口腔咽頭カンジダ症の治療：ポサコナゾールは400 mg（10 mL）を1日2回服用すること。

(3)　侵襲性真菌症の予防

ポサコナゾールは200 mg（5 mL）を1日3回服用すること。投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。

ポサコナゾール経口懸濁液の各投与は、食事とともに服用すること。
食事ができない患者では、曝露量を高めるために栄養補助剤と同時に服用すること。
投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。

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2)　ポサコナゾール徐放錠の用法

(1)　難治性侵襲性真菌症／不耐容の侵襲性真菌症の治療

初日に負荷用量として300 mg（100 mg 徐放錠3錠）を1日2回、その後は300 mg（100 mg 徐放錠3錠）を1日1回服用すること。各投与は食事の摂取に関係なく服用できる。投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。

(2)　侵襲性真菌症の予防

初日に負荷用量として300 mg（100 mg 徐放錠3錠）を1日2回、その後は300 mg（100 mg 徐放錠3錠）を1日1回服用すること。投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。

ポサコナゾール徐放錠は食事の摂取に関係なく服用できる。

3)　腎機能障害を有する患者への投与

腎機能障害を有する患者に対する用量調整は不要である。ポサコナゾールは腎排泄に大きくは依存せず、重度の腎機能障害がポサコナゾールの薬物動態に影響を及ぼさないと考えられることから、用量調整の推奨はない。曝露量にばらつきが認められるため、重度の腎機能障害を有する患者に投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること。

4)　肝機能障害を有する患者への投与

肝機能障害を有する患者での薬物動態データは限られているため、用量調整に関する推奨事項は設けていない。検討した少数の肝機能障害を有する患者において、肝機能低下に伴う半減期延長が認められた。

5)　小児への投与

13歳未満の小児に対する安全性及び有効性は確立されていない。

6)　高齢者への投与

高齢患者に対する用量調整の推奨はない。

禁忌

ポサコナゾールは、ポサコナゾール又はいずれかの添加剤に対して過敏症のある患者には禁忌である。

ポサコナゾールは麦角アルカロイドの血漿中濃度を増加させ、麦角中毒をもたらす可能性があるため、ポサコナゾールと麦角アルカロイド（エルゴタミン、ジヒドロエルゴタミン）の併用は禁忌である。

主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤とポサコナゾールの併用により、こ

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れらの薬剤の血漿中濃度が増加し、横紋筋融解症に至ることがあるため、両薬剤の併用は禁忌である。

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールと CYP3A4により代謝される特定の薬剤（テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン）の併用により、これらの薬剤の血漿中濃度が増加し、QT 延長及びまれにトルサード ド ポアントを引き起こすなど、場合によっては重篤な又は生命を脅かす有害事象につながる可能性がある。

警告及び使用上の注意

1)　過敏症

ポサコナゾールと他のアゾール系抗真菌薬との交差過敏症に関する情報はない。他のアゾール系抗真菌薬に対し過敏症のある患者にポサコナゾールを処方する場合は注意すること。アゾール系抗真菌薬に対して重度の又は重篤な反応をする患者は、ポサコナゾールの主要試験から除外していた。

2)　肝毒性

臨床試験では、ポサコナゾール投与中の肝機能障害（ALT、AST、ALP 及び総ビリルビンの軽度から中等度の増加、肝炎など）の発現割合は低かった。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もおり、投与中止を要することはまれであった。重篤な基礎疾患（例：血液悪性腫瘍）を有する患者で、ポサコナゾール投与期間中に死亡に至る、より重症の肝機能障害がまれに認められた。臨床薬理試験では、肝機能検査値に CTC Grade 3又は4［基準値上限（ULN）の5倍超］の上昇が認められた健康被験者は認められなかった。肝機能検査値の変化は大半が軽度であり、いずれも一過性で投与中止後にベースライン値まで回復し、試験中止に至ることはまれであった。健康被験者で認められた肝酵素異常を[表 1.6-19]に示す。

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表 1.6-19　　健康被験者で認められた肝酵素異常の概要（原文 Table 8）

CTC Grade	AST		ALT		GGT	
	ポサコナゾール 経口懸濁液 n=444	プラセボ n=48	ポサコナゾール 経口懸濁液 n=444	プラセボ n=48	ポサコナゾール 経口懸濁液 n=431	プラセボ n=47
0 (≤1×ULN)	417 (94%)	48 (100%)	388 (87%)	46 (96%)	408 (95%)	46 (98%)
1 (>1~2.5×ULN)	26 (6%)	0 (0%)	50 (11%)	1 (2%)	20 (5%)	1 (2%)
2 (>2.5~5×ULN)	1 (<1%)	0 (0%)	6 (1%)	1 (2%)	3 (1%)	0 (0%)

CTC：共通毒性基準、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、GGT：γ-グルタミルトランスフェラーゼ、ULN：基準値上限
注：被験者の大半はベースライン時の肝機能検査値の CTC Grade が0であった。本表には、投与期間中に各被験者で認められた各検査で最も悪い CTC Grade を要約している。本概要には、投与開始後の検査値が1時点以上得られた被験者のみを含めている。

3)　QTc 延長

一部のアゾール系抗真菌薬では、心電図での QTc 延長を引き起こすことがある。催不整脈状態にある患者へのポサコナゾールの投与には注意が必要である。CYP3A4により代謝される、QTc 間隔を延長させることが知られている薬剤とポサコナゾールを併用しないこと。

電解質障害：特に、カリウム、マグネシウム及びカルシウムの血中濃度をポサコナゾール治療開始前及び治療中にモニタリングし、必要に応じて治療すること。

4)　ビンクリスチンの毒性

ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

5)　生殖能への影響

雄ラットにポサコナゾールを最高180 mg/kg/日（健康被験者に高脂肪食摂取後に最高臨床推奨用量を投与した際の定常状態における AUC の1.6倍に相当）を投与したところ、生殖能への影響は認められなかった。ポサコナゾールを経口投与した雄イヌでは、他のアゾール系抗真菌薬と同様、精子巨細胞の出現など、テストステロンの血漿中濃度低下と一致する所見が認められた（曝露比4.2）。雌ラットにポサコナゾールを最高45 mg/kg/日（曝露比2.0）まで交配前2週間投与したところ、生殖能への影響は認められなかったが、4週間投与した雌ラットには発情周期異常が認められた。

6)　妊婦への投与

胎児危険度分類 B3：妊婦を対象とした適切な試験は実施されていない。ポサコナゾール経口懸濁液を投与された女性被験者で計3件の妊娠が報告されている。2件は中絶が選択され、

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胎児に対する検査の報告はなかった。残り1件は、同種 HSCT を受けた患者がポサコナゾール経口懸濁液200 mg の1日3回16週間の予防投与を完了し、約1ヵ月後の追跡調査のため来院した際に診断された妊娠であった。この妊婦は帝王切開により健康な男児を満期出産した。

ラットに経口投与した試験では、ヒトでの臨床推奨用量で予想される曝露量よりも低い曝露量において、着床後死亡、骨格変異増加、催奇形性（頭蓋顔面奇形）、妊娠期間延長、難産及び出生後生存率の低下などの生殖毒性が示された。ウサギでは、ヒトに治療用量のポサコナゾール経口懸濁液を投与したときよりも高い血漿中曝露量において、着床後死亡増加及び骨格変異増加が認められた。

母親への治療上の有益性が胎児への危険性を明らかに上回る場合を除き、ポサコナゾールを妊娠中に投与してはならない。妊娠可能な女性には、投与期間中及び投与完了後2週間以上は有効な避妊法を使用するよう指導しなければならない。

7)　授乳婦への投与

ポサコナゾールは授乳期ラットの乳汁中に移行する。ヒト乳汁中へのポサコナゾールの移行は検討していない。ポサコナゾールを服用中の女性は授乳してはならない。

8)　小児への投与

13歳未満の小児患者に対する安全性及び有効性は確立されていない。

13～17歳の小児患者に対するポサコナゾール経口懸濁液の臨床使用経験はごく限られているため（16例）、この年齢層の小児に対する薬理学、有効性及び安全性プロファイルは十分には解明されていない。得られているデータからは、13～17歳の小児と成人でのプロファイルと同様であることが示唆されている。

13～17歳の小児患者に対するポサコナゾール徐放錠の投与は、適切かつ十分にコントロールされたポサコナゾール経口懸濁液の試験で得られたエビデンスによって支持される。

9)　高齢者への投与

高齢患者に対する用量調整の推奨はない。

ポサコナゾール徐放錠を投与した230例中38例（17%）が65歳を超えていた。ポサコナゾール徐放錠の薬物動態は、若年被験者と高齢被験者で同様であった。全般的に高齢患者と若年患者で安全性に違いは認められなかったため、高齢患者に対する用量調整の推奨はない。

10)　副腎ステロイドホルモンへの影響

他のアゾール系抗真菌薬と同様に、ポサコナゾールの反復投与毒性試験でも副腎ステロイドホルモンの合成阻害に関連した影響が認められた。ラット及びイヌを用いた毒性試験では、ヒトに治療用量を投与した際に得られるのと同等以上の曝露量で副腎抑制作用が認められた。

11)　がん原性

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マウスにポサコナゾールを経口投与したところ、ヒトに最大臨床推奨用量を投与した際に予想される血漿中曝露量よりも約7倍高い血漿中曝露量で肝細胞腺腫が増加した。マウスはこうした腫瘍性変化に対する感受性が特に高いことが知られており、本所見はマウスにおける肝毒性に続発したものと判断した。

ラットにポサコナゾールを経口投与したところ、ヒトに対する投与時の 2.4 倍以上の曝露量で副腎皮質細胞腺腫及び副腎皮質細胞癌、並びに褐色細胞腫が認められた。こうした皮質の腫瘍は、副腎ステロイド産生の慢性的な機能障害後の内分泌異常と一致している。褐色細胞腫の増加は、カルシウム恒常性の変化に続発するラット特有の現象であると考えられている。ポサコナゾール経口懸濁液を投与したヒトでは、カルシウム恒常性の変化は認められていない。動物試験の結果から、ポサコナゾールの臨床使用によるがん原性リスクはほとんどないことが示されている。

12) 遺伝毒性

一連の *in vitro* 試験（細菌を用いた遺伝子突然変異試験、哺乳類を用いた遺伝子突然変異試験及びヒトリンパ球を用いた染色体異常試験）及び *in vivo* マウス小核試験において、ポサコナゾールの遺伝毒性が検討されている。こうした試験条件下でポサコナゾールは遺伝的損傷をもたらさなかった。

薬物相互作用

表 1.6-20　　薬物相互作用の概要（原文 Table 9）

禁忌	治療上の有益性が危険性を上回る場合を除き、併用を避ける	他剤を用量調整する、又は有害事象をモニタリング	用量調整の必要なし
・ エルゴタミン ・ ジヒドロエルゴタミン ・ テルフェナジン ・ アステミゾール ・ シサプリド ・ ピモジド ・ キニジン ・ Halofantrine ・ 主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤	・ リファブチン ・ フェニトイン ・ シメチジン ・ エファビレンツ ・ ビンカアルカロイド	・ リファブチン ・ シクロスポリン ・ タクロリムス ・ シロリムス ・ ミダゾラム ・ アタザナビル／リトナビル ・ ホスアンプレナビル ・ CYP3A4により代謝されるカルシウムチャネル遮断薬 ・ スルホニル尿素薬 ・ ジゴキシン	・ 制酸剤 ・ ジドブジン ・ リトナビル ・ ラミブジン ・ インジナビル ・ Glipizide

薬物相互作用試験の大半は、健康被験者にポサコナゾール経口懸濁液400 mg を1日2回食事又は栄養補助剤とともに反復投与して実施したことに留意すること。詳細な情報は以下を参照のこと。

1)　他剤のポサコナゾールへの影響

ポサコナゾールはウリジン5’-二リン酸-グルクロン酸転移酵素（第Ⅱ相代謝酵素）により代謝

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され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程を阻害又は誘導する薬剤により、血漿中ポサコナゾール濃度が影響を受ける可能性がある。

(1) リファブチン

リファブチン（300 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ43%及び49%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとリファブチンとの併用は避けること。

(2) フェニトイン

フェニトイン（200 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ41%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとフェニトインとの併用は避けること。

(3) シメチジン

シメチジン（400 mg 1日2回）により、ポサコナゾール経口懸濁液（200 mg 1日1回）の C_{max} 及び AUC は、それぞれ39%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとシメチジンとの併用は避けること。胃酸を抑制する可能性があるその他の H_2受容体拮抗薬及びプロトンポンプ阻害薬の影響は検討されていない。バイオアベイラビリティが低下するおそれがあるため、ポサコナゾールと H_2受容体拮抗薬又はプロトンポンプ阻害薬との併用は、可能な限り避けること。

(4) 制酸剤

ポサコナゾール経口懸濁液：制酸剤（25.4ミリ当量/5 mL の酸中和能に相当する液体の制酸剤）20 mL 単回投与はポサコナゾール経口懸濁液の C_{max} 及び AUC に臨床的に意義のある影響を及ぼさなかった。したがって、ポサコナゾールの用量調整は不要である。

ポサコナゾール徐放錠：制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬とポサコナゾール徐放錠との併用により、ポサコナゾールの薬物動態に臨床的に関連する影響は認められなかった。したがって、制酸剤、H_2受容体拮抗薬及びプロトンポンプ阻害薬との併用に際し、ポサコナゾール徐放錠の用量調整の必要はない。

(5) Glipizide

Glipizide（10 mg 単回投与）によるポサコナゾールの C_{max} 及び AUC への臨床的に意義のある影響は認められなかった。したがって、ポサコナゾールの用量調整は不要である。

(6) リトナビル

リトナビル（600 mg 1日2回）によるポサコナゾールの C_{max} 及び AUC への臨床的に意義

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のある影響は認められなかった。したがって、ポサコナゾールの用量調整は不要である。

(7) エファビレンツ

エファビレンツ（400 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ45%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとエファビレンツとの併用は避けること。

(8) ホスアンプレナビル

ホスアンプレナビルとポサコナゾールの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ホスアンプレナビルとポサコナゾールの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。健康被験者20例を対象にした試験では、ホスアンプレナビルの反復投与（700 mg 1日2回10日間）により、ポサコナゾール（初日に200 mg を1日1回、2日目に200 mg を1日2回、以降400 mg を1日2回8日間）の C_{max} 及び AUC は、それぞれ21%及び23%低下した。ポサコナゾール単独をホスアンプレナビル併用と比較した際のポサコナゾールの C_{max} 及び AUC の幾何平均比は、それぞれ0.79（0.71～0.89）及び0.77（0.68～0.87）であった。

2)　ポサコナゾールの他剤への影響

ポサコナゾールの CYP 酵素系による代謝量は臨床的に意義のあるものではない。しかし、ポサコナゾールは CYP3A4の阻害剤となるため、CYP3A4により代謝される薬剤をポサコナゾールと併用した場合は、併用薬の血漿中濃度が増加する可能性がある。

(1) テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールとの併用により、CYP3A4により代謝される特定の薬剤（テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン等）の血漿中濃度が増加し、重篤な又は生命を脅かす有害事象（QT延長及びまれにトルサード ド ポアント）を引き起こす可能性がある。したがって、これらの薬剤とポサコナゾールの併用は禁忌である。

(2) 麦角アルカロイド

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こすことがある。麦角アルカロイドとポサコナゾールの併用は禁忌である。

(3) ビンカアルカロイド

ビンカアルカロイドの大半（例：ビンクリスチン及びビンブラスチン）は CYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な

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有害事象を引き起こすおそれがあることが知られている。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。このため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

(4) シクロスポリン

シクロスポリンの安定した用量を処方されていた心臓移植患者にポサコナゾール200 mgを1日1回反復投与した際、減量を必要とするシクロスポリンの血中濃度の増加が引き起こされた。有効性評価試験では、シクロスポリンの血中濃度の増加により腎毒性などの重篤な有害事象発現に至った複数症例及び白質脳症による死亡が1例報告された。既にシクロスポリンを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シクロスポリンの用量を減量すること（例：現行用量の約3/4）。また、ポサコナゾールの併用期間中及び中止する際はシクロスポリンの血中濃度を注意深くモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

(5) タクロリムス

ポサコナゾールとの併用によりタクロリムス（0.05 mg/kg 単回投与）の C_{max} 及び AUC は、それぞれ121%及び358%増加した。有効性評価試験では、入院又はポサコナゾールの投与中止に至った臨床的に意義のある薬物相互作用が報告された。既にタクロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、タクロリムスの用量を減量すること（例：現行用量の約1/3）。また、ポサコナゾールの併用期間中及び中止する際はタクロリムスの血中濃度を注意深くモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(6) シロリムス

健康被験者にポサコナゾール400 mg を1日2回16日間反復経口投与した際、シロリムス（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均6.7倍及び8.9倍に増加した。既にシロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シロリムスの用量を減量し（例：現行用量の約1/10）、シロリムスの全血中トラフ濃度を頻回にモニタリングすること。ポサコナゾールの開始時、併用中及び中止時にシロリムスの血中濃度を測定し、シロリムスの用量を適切に調整すること。

(7) リファブチン

ポサコナゾールとの併用により、リファブチンの C_{max} 及び AUC は、それぞれ31%及び72%増加した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとリファブチンとの併用は避けること。これらの薬剤を併用する場合は、全血球数及びリファブチン

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の血中濃度の増加に起因する副作用（例：ぶどう膜炎）を注意深くモニタリングすることを推奨する。

(8) ミダゾラム

健康被験者にポサコナゾール200 mg 又は400 mg を1日2回、高脂肪食摂取後に反復経口投与にて併用したところ、ミダゾラムの C_{max} は2.2倍（約7.03～15.4 ng/mL）、AUC は約5倍（約31.9～159 ng·h/mL）に著しく増加し、ミダゾラムの終末相 $t_{1/2}$の平均が8～10時間に延長した。CYP3A4により代謝されるベンゾジアゼピン系薬剤（ミダゾラムを含む）については、ポサコナゾールとの併用期間中、用量調整を考慮することを推奨する。

(9) ジドブジン、ラミブジン、リトナビル及びインジナビル

ジドブジン（300 mg 1日2回又は200 mg 8時間に1回）、ラミブジン（150 mg 1日2回）、リトナビル（600 mg 1日2回）又はインジナビル（800 mg 8時間に1回）を安定した用量で投与中の HIV 感染患者において、ポサコナゾールはこれらの薬剤の C_{max} 及び AUC に臨床的に意義のある影響を及ぼさなかった。ポサコナゾールの併用によりリトナビルの曝露量は30%増加したが、臨床的に意義はないと考えられた。

(10) 主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤

ポサコナゾールの反復経口投与（50、100及び200 mg 1日1回13日間）により、シンバスタチン（40 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均7.4～11.4倍及び5.7～10.6倍に増加した。スタチン系薬剤の血漿中濃度の増加は横紋筋融解症を引き起こすおそれがある。したがって、主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤とポサコナゾールとの併用は禁忌である。

CYP3A4により代謝されない HMG-CoA 還元酵素阻害剤との薬物相互作用は検討されていないが、臨床推奨用量投与時のポサコナゾールの血中濃度は CYP3A4以外の CYP 分子種を阻害しないことから、CYP3A4により代謝されない HMG-CoA 還元酵素阻害剤との臨床的に意義のある薬物相互作用は起こらないと考えられる。

(11) CYP3A4により代謝されるカルシウムチャネル遮断薬

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールの併用期間中はカルシウムチャネル遮断薬に関連する副作用及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を調整すること。

(12) ジゴキシン

ジゴキシンとポサコナゾールの併用により、ジゴキシンの血漿中濃度が増加することが報告されている。このため、ポサコナゾールによる治療を開始又は中止する際は、ジゴキ

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シンの血中濃度をモニタリングすること。

(13) スルホニル尿素薬

Glipizide をポサコナゾールと併用した際、一部の健康被験者でグルコースの血中濃度が低下した。糖尿病患者ではグルコースの血中濃度のモニタリングを推奨する。

(14) HIV プロテアーゼ阻害剤

HIV プロテアーゼ阻害剤は CYP3A4の基質であるため、ポサコナゾールとの併用によりこれらの HIV プロテアーゼ阻害剤の血漿中濃度の増加が予想される。健康被験者にポサコナゾールを反復経口投与（400 mg 1日2回7日間）した際、アタザナビル（300 mg 1日1回7日間）の C_{max} 及び AUC は、それぞれ平均2.6倍及び3.7倍に増加した。リトナビルによるブースト療法下（アタザナビル300 mg 及びリトナビル100 mg の1日1回7日間併用）では、ポサコナゾール反復経口投与（400 mg 1日2回7日間）によるアタザナビルの C_{max} 及び AUC の増加はそれぞれ平均1.5倍及び2.5倍であり、リトナビルを併用しない場合と比較して増加の程度は小さかった。したがって、ポサコナゾールの併用期間中は、CYP3A4の基質である HIV プロテアーゼ阻害剤に関連する副作用及び毒性を頻回にモニタリングすることを推奨する。

(15) ホスアンプレナビル

ホスアンプレナビルをリトナビルと併用した際のホスアンプレナビルの血中濃度に対するポサコナゾールの影響は不明である。健康被験者20例を対象にした試験では、ポサコナゾール（初日に200 mg を1日1回、2日目に200 mg を1日2回、以降400 mg を1日2回8日間）をホスアンプレナビル（700 mg 1日2回10日間）と併用した際、アンプレナビルの C_{max} 及び AUC は、ホスアンプレナビルとリトナビルの併用時と比べてそれぞれ36%及び65%低下した。ホスアンプレナビルとリトナビルの併用時に対する、ホスアンプレナビルとポサコナゾール併用時のアンプレナビルの C_{max} 及び AUC の幾何平均比は、それぞれ0.64（0.55～0.76）及び0.35（0.32～0.39）であった。

有害事象

1)　ポサコナゾール経口懸濁液

ポサコナゾール経口懸濁液を投与した2,400例で認められた副作用を[表 1.6-21]に示す。172例が6ヵ月以上、58例が12ヵ月以上の投与を受けた。

健康被験者と患者の全集団で認められた副作用で発現割合が高い事象は、悪心（6%）及び頭痛（6%）であった。

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表 1.6-21　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 10）

よくみられる（>1/100、<1/10）、あまりみられない（>1/1,000、<1/100）、まれな（>1/10,000、<1/1,000）

感染症および寄生虫症	
あまりみられない：	口腔カンジダ症、副鼻腔炎
まれな：	カテーテル関連感染、疱疹性以外の口唇ヘルペス、食道カンジダ症、肺炎、上気道感染、尿路感染
血液およびリンパ系障害	
よくみられる：	好中球減少症
あまりみられない：	貧血、血小板減少症、白血球減少症、好酸球増加症、リンパ節症
まれな：	血液ガス異常、溶血性尿毒症症候群、好中球増加症、汎血球減少症、凝固障害、出血 NOS、血小板数増加、プロトロンビン減少、プロトロンビン時間延長、紫斑、血栓性血小板減少性紫斑病
免疫系障害	
あまりみられない：	アレルギー反応
まれな：	過敏症反応、スティーヴンス・ジョンソン症候群
内分泌障害	
まれな：	副腎機能不全、ゴナドトロピン減少
代謝および栄養障害	
よくみられる：	食欲不振、電解質失調
あまりみられない：	高血糖、高トリグリセリド血症、高尿酸血症、体重減少、LDH 増加、脱水
まれな：	アミラーゼ増加、高コレステロール血症、高脂血症、高蛋白血症、低アルブミン血症、リパーゼ増加、代謝性アシドーシス、腎尿細管性アシドーシス、ビタミン K 欠乏、体重増加
精神障害	
あまりみられない：	精神状態変化、不安、錯乱、不眠症
まれな：	健忘、うつ病、異常な夢、情動不安定、リビドー減退、魔夢、精神病
神経系障害	
よくみられる：	浮動性めまい、頭痛、錯感覚、傾眠
あまりみられない：	ニューロパチー、感覚鈍麻、痙攣、振戦
まれな：	末梢性ニューロパチー、反射消失、運動失調、認知障害、譫妄、発声障害、ジストニア、脳症、不全片麻痺、運動過多、反射亢進、反射減弱、筋緊張低下、集中力障害、記憶障害、髄膜症、単神経炎、下肢静止不能症候群、坐骨神経痛、失神
眼障害	
あまりみられない：	結膜炎、霧視
まれな：	眼痛、眼乾燥、眼窩周囲浮腫、複視、羞明、暗点
耳および迷路障害	
あまりみられない：	耳痛、回転性めまい
まれな：	聴力障害、耳鳴
心臓障害	
あまりみられない：	ECG 異常、QT/QTc 延長、心房粗動、心房細動、脚ブロック、頻脈、期外収縮、動悸、心室肥大
まれな：	徐脈、心不全、心肺停止、突然死、心室性頻脈、大動脈弁硬化症、心拡大、駆出率減少、僧帽弁疾患 NOS、心筋梗塞、上室性頻脈、心房性期外収縮、心室性期外収縮、AV ブロック、トルサード ド ポアント

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表 1.6-21　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 10）（続き）

血管障害	
あまりみられない：	潮紅、ほてり、高血圧、低血圧
まれな：	アテローム性動脈硬化症、脳血管発作、深部静脈血栓症 NOS、肺塞栓症、虚血、血腫
呼吸器、胸郭および縦隔障害	
あまりみられない：	胸痛、咳嗽、呼吸困難、鼻出血、咽頭炎、鼻閉
まれな：	無気肺、咽喉乾燥、肺高血圧症、間質性肺炎、鼻刺激感、肺臓炎、後鼻漏、肺浸潤、ラ音、鼻炎、鼻漏
胃腸障害	
よくみられる：	腹痛、下痢、消化不良、鼓腸、口内乾燥、悪心、嘔吐
あまりみられない：	味覚倒錯、便秘、ゆるい便、腹部膨満、嚥下障害、腹水、おくび、口渇、胃炎、胃食道逆流、粘膜炎 NOS、食道炎、膵炎、舌変色
まれな：	胃腸管出血、イレウス、腹部圧痛、口唇炎、血性下痢、食道潰瘍形成、出血性胃炎、嚥下痛、膵酵素 NOS 増加、肛門周囲痛、レッチング、アフタ性口内炎、しぶり、メレナ、歯肉炎、舌炎
肝胆道系障害	
よくみられる：	肝機能検査値（AST、ALT、ALP、GGT、ビリルビン等）上昇
あまりみられない：	肝炎、肝細胞損傷、肝腫大、黄疸
まれな：	固定姿勢保持困難、胆汁うっ滞、肝不全、胆汁うっ滞性肝炎、肝脾腫大、肝圧痛、脾腫
皮膚および皮下組織障害	
よくみられる：	発疹
あまりみられない：	脱毛症、皮膚乾燥、斑状丘疹状皮疹、蕁麻疹、せつ腫症、ざ瘡、口腔内潰瘍形成、そう痒症、そう痒性皮疹
まれな：	口内炎、皮膚炎、紅斑、紅斑性皮疹、毛孔性皮疹、斑状皮疹、寝汗、脂漏、皮膚小結節、小水疱性皮疹
筋骨格系および結合組織障害	
あまりみられない：	筋肉痛、関節痛、背部痛、筋骨格痛、側腹部痛、筋力低下
まれな：	骨痛、胸壁痛、筋膜炎、頚部硬直、四肢痙攣、筋痙攣
腎および尿路障害	
あまりみられない：	アルブミン尿、排尿回数変化、排尿困難、血中クレアチニン増加、急性腎不全、腎不全、血尿、腎機能障害、夜間頻尿
まれな：	BUN 増加、間質性腎炎、排尿異常、腎結石、尿路閉塞 NOS
生殖系および乳房障害	
あまりみられない：	月経障害
まれな：	白帯下、乳房痛
一般・全身障害および投与部位の状態	
よくみられる：	無力症、疲労、発熱
あまりみられない：	多汗、疼痛、悪寒、倦怠感、脱力、浮腫、変色歯
まれな：	顔面浮腫、舌浮腫
臨床検査	
あまりみられない：	薬物濃度変化
傷害、中毒および処置合併症	
あまりみられない：	薬物毒性 NOS
まれな：	斑状出血

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表 1.6-21　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 10）（続き）

NOS：他に特定されない、LDH：乳酸脱水素酵素、ECG：心電図、QTc：心拍数補正 QT 間隔、AV：房室、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、ALP：アルカリホスファターゼ、GGT：γ-グルタミルトランスフェラーゼ、BUN：尿素窒素

重篤な副作用は、難治性侵襲性真菌症患者の併合集団の8%（35/428例）で認められた。個々の重篤な副作用の大半は発現割合が1%未満であり、大部分が侵襲性真菌症を発症する素因となる重篤な基礎疾患を反映する事象であった。発現割合が1%（3又は4例）の重篤な副作用は、他剤の薬物濃度変化、肝酵素上昇、悪心、発疹及び嘔吐であった。一方、予防のためポサコナゾール経口懸濁液を投与された患者605例でみられた重篤な副作用は、ビリルビン血症、肝酵素上昇、肝細胞損傷、悪心及び嘔吐（各1%）などであった。

ポサコナゾール経口懸濁液での臨床試験中にみられた、まれで医学的に意味のある副作用は、副腎機能不全、膵炎、アレルギー又は過敏症反応などであった。

一部のアゾール系抗真菌薬は、心電図の QT 延長を引き起こすことが知られている。ポサコナゾール経口懸濁液を投与された健康被験者173例において測定時間を一致させた心電図の併合解析では、QT 間隔を延長させる可能性は示されなかった。なお、ポサコナゾール経口懸濁液を投与された患者でのトルサード ド ポアントの報告はまれであった。

さらに、主に移植後の拒絶反応又は移植片対宿主病の管理のためシクロスポリン又はタクロリムスを併用している患者に、溶血性尿毒症症候群及び血栓性血小板減少性紫斑病がまれに認められた。

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表 1.6-22　　ポサコナゾール経口懸濁液を投与された侵襲性真菌症患者における発現割合 1%以上の副作用（程度は治験担当医師判定に基づく）（原文 Table 11）

事象名	すべての副作用 n=330 発現例数（%）	軽度／中等度のすべての副作用 n=330 発現例数（%）	重度／生命を脅かすすべての副作用 n=330 発現例数（%）
一般的全身障害			
食欲不振	8 (2)	8 (2)	0
無力症	4 (1)	4 (1)	0
胸痛	2 (1)	2 (1)	0
浮動性めまい	7 (2)	6 (2)	1 (<1)
薬物濃度変化	7 (2)	4 (1)	3 (1)
疲労	7 (2)	6 (2)	1 (<1)
発熱	3 (1)	3 (1)	0
頭痛	15 (5)	13 (4)	2 (1)
脱力	2 (1)	2 (1)	0
心・血管障害（一般）			
心肺停止	2 (1)	0	2 (1)
心室肥大	2 (1)	1 (<1)	1 (<1)
中枢・末梢神経系障害			
錯乱	3 (1)	3 (1)	0
痙攣	2 (1)	0	2 (1)
反射亢進	2 (1)	2 (1)	0
感覚鈍麻	2 (1)	2 (1)	0
精神状態変化	2 (1)	2 (1)	0
錯感覚	6 (2)	6 (2)	0
傾眠	3 (1)	3 (1)	0
振戦	2 (1)	2 (1)	0
血液およびリンパ系障害	6 (2)	4 (1)	2 (1)
貧血	4 (1)	3 (1)	1 (<1)
眼障害	4 (1)	3 (1)	1 (<1)
霧視	2 (1)	2 (1)	0
生殖系および乳房障害			
乳房痛	1 (<1)	1 (<1)	0
月経障害（女性のみに基づく）	2 (2)	2 (2)	0
消化管障害			
腹部膨満	2 (1)	2 (1)	0
腹痛	16 (5)	13 (4)	3 (1)
便秘	2 (1)	2 (1)	0
下痢	11 (3)	10 (3)	1 (<1)
消化不良	2 (1)	2 (1)	0
鼓腸	3 (1)	3 (1)	0
口内乾燥	5 (2)	5 (2)	0
悪心	31 (9)	2 (1)	29 (9)
嘔吐	19 (6)	18 (5)	1 (<1)
心拍数・心リズム障害			
心房粗動	2 (1)	1 (<1)	1 (<1)
特異的 ECG 異常	2 (1)	2 (1)	0
期外収縮	2 (1)	1 (<1)	1 (<1)
心房細動	3 (1)	2 (1)	1 (<1)
QT/QTc 延長	6 (2)	6 (2)	0
頻脈	2 (1)	2 (1)	0
上室性頻脈	2 (1)	1 (<1)	1 (<1)
傷害及び中毒			
薬物毒性 NOS	2 (1)	0	2 (1)
肝臓・胆管系障害			
ビリルビン血症	4 (1)	3 (1)	1 (<1)

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表 1.6-22　　ポサコナゾール経口懸濁液を投与された侵襲性真菌症患者における発現割合 1%以上の副作用（程度は治験担当医師判定に基づく）（原文 Table 11）（続き）

事象名	すべての副作用 n=330 発現例数（%）	軽度／中等度のすべての副作用 n=330 発現例数（%）	重度／生命を脅かすすべての副作用 n=330 発現例数（%）
γ-GT 増加	2 (1)	0	2 (2)
肝酵素上昇	7 (2)	6 (2)	1 (<1)
肝機能異常	2 (1)	2 (1)	0
黄疸	2 (1)	1 (<1)	1 (<1)
AST 増加	9 (3)	6 (2)	3 (1)
ALT 増加	11 (3)	9 (3)	2 (1)
代謝・栄養障害			
アルカリホスファターゼ増加	6 (2)	5 (2)	1 (<1)
口渇	2 (1)	2 (1)	0
筋・骨格系障害			
筋骨格痛	2 (1)	2 (1)	0
血小板・出血凝血障害			
血小板減少症	2 (1)	2 (1)	0
腎および尿路障害			
血中クレアチニン減少	5 (2)	4 (2)	1 (<1)
夜間頻尿	2 (1)	2 (1)	0
腎不全	2 (1)	1 (<1)	1 (<1)
急性腎不全	2 (1)	0	2 (1)
皮膚および皮下組織障害			
脱毛症	4 (1)	4 (1)	0
皮膚乾燥	3 (1)	3 (1)	0
そう痒症	3 (1)	3 (1)	0
発疹	9 (3)	7 (2)	2 (1)
斑状丘疹状皮疹	4 (1)	3 (1)	1 (<1)
小水疱性皮疹	2 (1)	2 (1)	0

ECG：心電図、QTc：心拍数補正 QT 間隔、NOS：他に特定されない、GT：グルタミルトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ

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表 1.6-23　　ポサコナゾール経口懸濁液を投与された口腔咽頭カンジダ症患者における発現割合 2%以上の副作用（すべてのグレード）（原文 Table 12）

事象名	患者数（%）		
	OPC 比較試験データの併合		難治性 OPC 試験データの併合
	ポサコナゾール 経口懸濁液 n=557	フルコナゾール n=262	ポサコナゾール 経口懸濁液 n=239
有害事象が認められた患者†	150 (27)	70 (27)	135 (56)
一般的全身障害			
食欲不振	6 (1)	1 (<1)	7 (3)
無力症	4 (1)	2 (1)	6 (3)
浮動性めまい	9 (2)	5 (2)	8 (3)
疲労	8 (1)	5 (2)	7 (3)
発熱	10 (2)	1 (<1)	6 (3)
頭痛	16 (3)	5 (2)	18 (8)
中枢・末梢神経系障害			
傾眠	4 (1)	5 (2)	3 (1)
血液およびリンパ系障害			
貧血	2 (<1)	0 (0)	6 (3)
好中球減少症	10 (2)	4 (2)	20 (8)
消化管障害			
腹痛	10 (2)	8 (3)	12 (5)
下痢	19 (3)	13 (5)	26 (11)
鼓腸	6 (1)	0 (0)	11 (5)
口内乾燥	7 (1)	6 (2)	5 (2)
悪心	27 (5)	18 (7)	20 (8)
嘔吐	20 (4)	4 (2)	16 (7)
肝臓・胆管系障害			
肝酵素上昇	1 (<1)	0 (0)	5 (2)
肝機能異常	3 (1)	4 (2)	0 (0)
代謝・栄養障害			
アルカリホスファターゼ増加	3 (1)	3 (1)	5 (2)
筋・骨格系障害			
筋肉痛	1 (<1)	0 (0)	4 (2)
血小板・出血凝血障害			
血小板減少症	3 (1)	0 (0)	4 (2)
精神障害			
不眠症	3 (1)	0 (0)	6 (3)
皮膚および皮下組織障害			
そう痒症	6 (1)	2 (1)	5 (2)
発疹	8 (1)	4 (2)	10 (4)

OPC：口腔咽頭カンジダ症
† 試験期間中に有害事象が1件以上認められた患者数。事象が複数回認められた患者がいる可能性もある。

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表 1.6-24　　CI98-316 試験及び P01899 試験
ポサコナゾール経口懸濁液又はフルコナゾールの予防投与患者における
発現割合 2%以上のすべての副作用及び重度／生命を脅かす副作用の発現例数（%）（原文 Table 13）

	ポサコナゾール 経口懸濁液 n=605		フルコナゾール n=539		イトラコナゾール n=58	
	すべての副作用	重度／生命を脅かす副作用	すべての副作用	重度／生命を脅かす副作用	すべての副作用	重度／生命を脅かす副作用
副作用が認められた患者†	209 (35)	81 (13)	186 (35)	53 (10)	30 (52)	6 (10)
消化管障害						
腹痛	13 (2)	1 (<1)	15 (3)	2 (<1)	1 (2)	0
便秘	4 (1)	0	12 (2)	0	0	0
下痢	28 (5)	4 (1)	24 (4)	1 (<1)	9 (16)	0
消化不良	8 (1)	1 (<1)	9 (2)	0	0	0
悪心	44 (7)	5 (1)	45 (8)	1 (<1)	8 (14)	0
嘔吐	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
心拍数・心リズム障害						
QT/QTc 延長	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
肝臓・胆管系障害						
ビリルビン血症	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT 増加	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
肝酵素上昇	15 (2)	11 (2)	10 (2)	3 (1)	0	0
AST 増加	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
ALT 増加	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	1 (2)
代謝・栄養障害						
低カリウム血症	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
皮膚および皮下組織障害						
発疹	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

QTc：心拍数補正 QT 間隔、GGT：γ-グルタミルトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ
† 試験期間中に副作用が1件以上認められた患者数。事象が複数回認められた患者がいる可能性もある。

2)　ポサコナゾール徐放錠

ポサコナゾール徐放錠の臨床試験で報告された有害事象の種類及び発現割合は、ポサコナゾール経口懸濁液で報告されたものと概して同様であった。

臨床試験で患者230例を対象にポサコナゾール徐放錠の安全性を評価した。患者は真菌症予防を目的としたポサコナゾール徐放錠の薬物動態及び安全性評価の非対照試験（P05615試験）に組み入れられた。患者は血液悪性腫瘍、化学療法後好中球減少症、移植片対宿主病、HSCT 後などの基礎疾患を伴う免疫不全状態にあった。この患者集団では、男性62%、平均年齢51歳（範囲：19～78歳、65歳以上：17%）、白人93%、ヒスパニック系16%であった。ポサコナゾールの投与期間の中央値は28日間であった。用量は20例が200 mg/日、210例が300 mg/日であった（各コホートの投与初日は1日2回）。

ポサコナゾール徐放錠（300 mg 1日1回）でみられた副作用で発現割合が高い（5%以上）事象は、悪心及び下痢であった。ポサコナゾール徐放錠（300 mg 1日1回）で投与中止に至った有害事象で発現割合が最も高い事象は、悪心であった。

ポサコナゾール徐放錠の予防投与試験において、ポサコナゾール徐放錠300 mg/日を投与した

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患者に認められた発現割合10%以上の有害事象の発現例数を[表 1.6-25]に示す。

表 1.6-25　　ポサコナゾール徐放錠の P05615 試験
300 mg/日予防投与患者における発現割合 10%以上の有害事象の発現例数（%）（原文 Table 14）

器官別大分類 基本語	ポサコナゾール徐放錠（300 mg） (n=210)	
有害事象が認められた患者	201	(99)
血液およびリンパ系障害		
貧血	22	(10)
発熱性好中球減少症	42	(20)
血小板減少症	29	(14)
胃腸障害		
腹痛	23	(11)
便秘	20	(10)
下痢	61	(29)
悪心	56	(27)
嘔吐	28	(13)
一般・全身障害および投与部位の状態		
無力症	20	(10)
カテーテル留置部位紅斑	20	(10)
悪寒	22	(10)
粘膜の炎症	29	(14)
末梢性浮腫	33	(16)
発熱	59	(28)
代謝および栄養障害		
低カリウム血症	46	(22)
低マグネシウム血症	20	(10)
神経系障害		
頭痛	30	(14)
呼吸器、胸郭および縦隔障害		
咳嗽	35	(17)
鼻出血	30	(14)
皮膚および皮下組織障害		
発疹	34	(16)
血管障害		
高血圧	23	(11)

3)　臨床検査値

侵襲性真菌症患者にポサコナゾール経口懸濁液800 mg/日を投与した（非対照）試験での臨床的に意義のある肝機能検査異常の発現割合は、ALT 及び AST［基準値上限（ULN）の3倍超］がそれぞれ11%及び10%、総ビリルビン（ULN の1.5倍超）が22%、ALP（ULN の3倍超）が14%であった。健康被験者で認められた肝酵素上昇は血漿中ポサコナゾール濃度の高値と関連しないと考えられた。患者で認められた大多数の肝機能検査異常は軽微で一過性の変化であり、投与中止に至ることはまれであった。

HIV 感染患者にポサコナゾールを最高400 mg まで投与した比較試験での臨床的に意義のある肝機能検査異常の発現割合は、ALT 及び AST（ULN の3倍超）がそれぞれ3%及び6%、総ビリ

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ルビン（ULN の1.5倍超）が3%、ALP（ULN の3倍超）が3%であった。

予防投与試験（CI98-316試験及び P01899試験）で共通毒性基準（CTC）に基づく肝機能検査値が、ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数を[表1.6-26]に示す。

表 1.6-26　　ポサコナゾール経口懸濁液 CI98-316 試験及び P01899 試験 肝機能検査値がベースライン時の CTC Grade 0、1 又は 2 から Grade 3 又は 4 へ変化した患者数（原文 Table 15）

臨床検査値	変化が認められた患者数（%）†	
	ポサコナゾール経口懸濁液の試験（CI98-316試験）	
	ポサコナゾール n=301	フルコナゾール n=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
ビリルビン	24/271 (9)	20/275 (7)
ALP	9/271 (3)	8/271 (3)
	ポサコナゾール経口懸濁液の試験（P01899試験）	
	ポサコナゾール n=304	フルコナゾール／イトラコナゾール n=298
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
ビリルビン	20/290 (7)	25/285 (9)
ALP	4/281 (1)	1/276 (<1)

† ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数。X はその定義を満たす患者数、Y はベースライン値が得られ、かつベースライン後の1時点以上で検査値が得られた患者数として、X/Y の形式でデータを示す。
CTC：共通毒性基準、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、ALP：アルカリホスファターゼ

過量投与

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された被験者で発現した有害事象は、より低用量で認められたものと同様であった。また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

重度の血液透析依存腎機能障害を有する患者（クレアチニンクリアランス：<20 mL/min）を対象とした試験において、ポサコナゾールは血液透析で除去されなかった。そのため、血液透析はポサコナゾールを全身循環血から除去する上で有効ではないと考えられる。

ポサコナゾール徐放錠の過量投与は報告されていない。

過量投与の管理について相談したい場合は、Poisons Information Centre（131126）に連絡すること。

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1.6.2.1.3.2　　静注用濃厚溶液

1. 販売名

Noxafil® 静注用濃厚溶液

2. 含量

ポサコナゾールは白色からオフホワイトの結晶粉末である。融点範囲は164°C から165°C であり、水に溶解しない。

ポサコナゾール静注用濃厚溶液の各バイアルは、ポサコナゾール300 mg（18 mg/mL）を含有する。

全添加剤の一覧は6.1項の**添加物の一覧**を参照すること。

3. 剤形

ポサコナゾール静注用濃厚溶液は澄明で無色から黄色の液体である。

4. 臨床的な特徴

4. 1　効能・効果

ポサコナゾール静注用濃厚溶液には、成人における以下の侵襲性真菌症の治療の適応がある：

- 他の治療が不耐容又は無効な疾患を有する患者における侵襲性アスペルギルス症
- 他の治療が不耐容又は無効な疾患を有する患者におけるフサリウム症、ムーコル症、コクシジオイデス症、クロモブラストミコーシス及び菌腫

ポサコナゾールには、以下の適応もある：

- 持続性好中球減少症患者又は造血幹細胞移植（HSCT）患者のような侵襲性真菌症を発症するリスクが高い成人における侵襲性真菌症の予防

4. 2　用法・用量

ポサコナゾールは、真菌症管理の経験、又はポサコナゾールが予防投与の適応とする疾患のリスクが高い患者での支持療法の経験が豊富な医師によって投与を開始すること。

適応症による推奨用量を[表 1.6-27]に示す。

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表 1.6-27　　適応症による推奨用量（原文 Table 1）

適応症	用法・用量
難治性侵襲性真菌症（IFI）／他の治療に不耐容の IFI の治療	初日に負荷用量として300 mg を1日2回、その後は300 mg を1日1回静脈内投与する。投与期間は患者の基礎疾患の程度、免疫抑制からの回復及び臨床効果に基づき設定すること。
侵襲性真菌症の予防	初日に負荷用量として300 mg を1日2回、その後は300 mg を1日1回静脈内投与する。投与期間は好中球減少症又は免疫抑制からの回復に基づき設定すること。AML 又は MDS 患者に対する予防投与は、好中球減少症の発現が予測される数日前から開始し、好中球数が500 cells/mm^{3}超に増加してから7日間継続すること。

1)　投与方法

ポサコナゾール静注用濃厚溶液は投与前に希釈しなければならない。急速静注は行わないこと。

- 冷蔵保存されていたポサコナゾールのバイアルを室温に戻す。
- 最終濃度（1 mg/mL を下回らず、2mg/mL を超えない）に応じて、ポサコナゾール16.7 mL を混合可能な静注溶液（下記参照）150 mL から283 mL 入れた点滴バッグ（又はボトル）に無菌的に移す。
- 中心静脈カテーテル又は末梢穿刺中心静脈カテーテルを含む中心静脈ラインから、約90分間かけて緩徐に点滴静注すること。急速静注は行わないこと。
- 中心静脈カテーテルが使用できない場合は、末梢静脈カテーテルから単回投与してもよい。末梢静脈カテーテルから注入する場合、約30分間かけて静注すること。
  注：臨床試験において、同一の静脈から反復末梢注入された患者での忍容性は不良であった［4.8項の**有害事象（意図しない反応）**を参照すること］。
- ポサコナゾールは保存剤を含まない一回使い切りの無菌溶液である。そのため、微生物学的観点から、希釈後は速やかに使用すること。速やかに使用しない場合は、2～8℃で24時間まで冷蔵保存可能である。ポサコナゾール静注用濃厚溶液は一回使い切りであり、残液は廃棄すること。

ポサコナゾール静注用濃厚溶液は以下で希釈可能である。

- 5%ブドウ糖液
- 0.9%塩化ナトリウム溶液
- 0.45%塩化ナトリウム溶液
- 5%ブドウ糖液／0.45%塩化ナトリウム溶液
- 5%ブドウ糖液／0.9%塩化ナトリウム溶液
- 5%ブドウ糖液／20ミリ当量塩化カリウム溶液

ポサコナゾール静注用濃厚溶液はこれらの希釈液のみと投与すること。

ポサコナゾール静注用濃厚溶液は、乳糖リンゲル液、5%ブドウ糖加乳糖リンゲル液、4.2%炭酸水素ナトリウム溶液で希釈してはならない。

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2)　希釈液との適合性

ポサコナゾール静注用濃厚溶液と注射製剤及び一般的に使用される静注用希釈液との適合性を評価するために、静注器具の側管からの擬似投与試験を実施した。適合性は外観、異物、濁度により評価した。

本試験の結果に基づくと、以下の薬剤は、ポサコナゾール静注用濃厚溶液と同一の静脈ライン（又はカニューレ）から同時に注入可能である。

表 1.6-28　　ポサコナゾール静注用濃厚溶液と同一ラインから同時に注入可能な薬剤（原文 3 ページ、Table 番号なし）

アミカシン硫酸塩
カスポファンギン
シプロフロキサシン
ダプトマイシン
ドブタミン塩酸塩
ファモチジン
フィルグラスチム
ゲンタマイシン硫酸塩
ヒドロモルホン塩酸塩
レボフロキサシン
ロラゼパム
メロペネム
ミカファンギン
モルヒネ硫酸塩
酒石酸水素ノルエピネフリン
塩化カリウム
バンコマイシン塩酸塩

上表に記載されていない薬剤は、ポサコナゾールと同一の静脈ライン（又はカニューレ）から同時に注入しないこと。

ポサコナゾール静注用濃厚溶液の投与前に目視で異物がないか確認すること。ポサコナゾールの溶液は無色から微黄色である。この範囲内の色のばらつきは本剤の品質に影響を及ぼさない。

3)　腎機能障害を有する患者への投与

中等度又は重度（eGFR：<50 mL/min/1.73 m^2）の腎機能障害を有する患者にポサコナゾール静注用濃厚溶液を投与した場合、基剤である SBECD が蓄積するおそれがある。中等度又は重度（eGFR：<50 mL/min/1.73 m^2）の腎機能障害を有する患者では、患者の有益性及び危険性を考慮して使用が正当化されない限り、ポサコナゾール静注用濃厚溶液の静脈内投与を避けること。これらの腎機能障害を有する患者では、血清クレアチニン値を慎重にモニタリングし、上昇が認められた場合には、ポサコナゾール経口懸濁液への切り替えを考慮すること。曝露量にばらつきが認められるため、重度の腎機能障害を有する患者に

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投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること（5.2項の**薬物動態的特徴**及び4.4項の**警告及び使用上の注意**を参照すること）。

4)　肝機能障害を有する患者への投与

肝機能障害を有する患者での薬物動態データは限られているため、用量調整に関する推奨事項は設けていない。検討した少数の肝機能障害を有する患者において、肝機能低下に伴う半減期延長が認められた（5.2項の**薬物動態的特徴**、**特別な背景をもつ患者における薬物動態**を参照すること）。

5)　小児への投与

18歳未満の小児に対する安全性及び有効性は確立されていない。

非臨床での安全上の問題から、ポサコナゾール静注用濃厚溶液は小児患者に投与しないこと（5.3項の**非臨床安全性データ**の**非臨床における安全性**を参照すること）。

6)　高齢者への投与

高齢患者に対する用量調整の推奨はない（5.2項の**薬物動態的特徴**の**特別な背景を持つ患者における薬物動態**を参照すること）。

4．3　禁忌

ポサコナゾールは、ポサコナゾール又はいずれかの添加剤に対して過敏症のある患者には禁忌である。

ポサコナゾールは麦角アルカロイドの血漿中濃度を増加させ、麦角中毒をもたらす可能性があるため、ポサコナゾールと麦角アルカロイド（エルゴタミン、ジヒドロエルゴタミン）の併用は禁忌である（4.5項の**他剤との相互作用やその他の相互作用**を参照すること）。

主にCYP3A4により代謝されるHMG-CoA還元酵素阻害剤とポサコナゾールの併用により、これらの薬剤の血漿中濃度が増加し、横紋筋融解症に至ることがあるため、両薬剤の併用は禁忌である。

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールとCYP3A4により代謝される特定の薬剤（テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン）の併用により、これらの薬剤の血漿中濃度が増加し、QT 延長及びまれにトルサード ド ポアントを引き起こすなど、場合によっては重篤な又は生命を脅かす有害事象につながる可能性がある（4.5項の**他剤との相互作用やその他の相互作用**を参照すること）。

4．4　警告及び使用上の注意

1)　過敏症

ポサコナゾールと他のアゾール系抗真菌薬との交差過敏症に関する情報はない。他のアゾール系抗真菌薬に対し過敏症のある患者にポサコナゾールを処方する場合は注意すること。アゾ

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ール系抗真菌薬に対して重度の又は重篤な反応をする患者は、ポサコナゾールの主要試験から除外していた。

2)　肝毒性

臨床試験では、肝機能障害（ALT、AST、ALP 及び総ビリルビンの軽度から中等度の増加、肝炎など）が報告されている。肝機能検査値の上昇は通常投与中止により回復したが、休薬せずに検査値が基準域に回復した患者もおり、投与中止を要することはまれであった。重篤な基礎疾患（例：血液悪性腫瘍）を有する患者で、ポサコナゾール投与期間中に死亡に至る、より重症の肝機能障害がまれに認められた。臨床薬理試験では、肝機能検査値に CTC Grade 3又は4［基準値上限（ULN）の5倍超］の上昇が認められた健康被験者は認められなかった。肝機能検査値の変化は大半が軽度であり、いずれも一過性で投与中止後にベースライン値まで回復し、試験中止に至ることはまれであった。健康被験者で認められた肝酵素異常の概要を[表 1.6-29]に示す。

ポサコナゾールの投与開始時と投与期間中（特に、ポサコナゾール静注用濃厚溶液の投与期間が14日間を超える場合）は肝機能検査値を評価すること。肝機能障害を有する患者での臨床使用経験は少なく、これらの患者ではポサコナゾールの血漿中濃度が高くなる可能性があるため、ポサコナゾールは慎重に投与すること。ポサコナゾールによる治療中に肝機能検査値が異常となった患者は、より重度の肝損傷が発現しないか観察すること。患者の管理には、肝機能の臨床評価（特に肝機能検査及びビリルビン）を含めること。臨床徴候・症状が肝疾患の発現時と同様となった場合には、ポサコナゾールの投与中止を検討すること。

表 1.6-29　　健康被験者で認められた肝酵素異常の概要（原文 Table 2）

CTC Grade	AST		ALT		GGT	
	ポサコナゾール経口懸濁液 n=444	プラセボ n=48	ポサコナゾール経口懸濁液 n=444	プラセボ n=48	ポサコナゾール経口懸濁液 n=431	プラセボ n=47
0 (≤1×ULN)	417 (94%)	48 (100%)	388 (87%)	46 (96%)	408 (95%)	46 (98%)
1 (>1~2.5×ULN)	26 (6%)	0 (0%)	50 (11%)	1 (2%)	20 (5%)	1 (2%)
2 (>2.5~5×ULN)	1 (<1%)	0 (0%)	6 (1%)	1 (2%)	3 (1%)	0 (0%)

CTC：共通毒性基準、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、GGT：γ-グルタミルトランスフェラーゼ、ULN：基準値上限
注：被験者の大半はベースライン時の肝機能検査値の CTC Grade が0であった。本表には、投与期間中に各被験者で認められた各検査で最も悪い CTC Grade を要約している。本概要には、投与開始後の検査値が1時点以上得られた被験者のみを含めている。

3)　QT 延長

一部のアゾール系抗真菌薬では、心電図での QTc 延長を引き起こすことがある。催不整脈状態にある患者へのポサコナゾールの投与には注意が必要である。CYP3A4により代謝される、QTc 間隔を延長させることが知られている薬剤とポサコナゾールを併用しないこと（5.2項の**薬物動態的特徴**の**心電図の評価**、4.3項の**禁忌**、4.5項の**他剤との相互作用及びその他の相互作用**を

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参照すること)。

電解質障害：特に、カリウム、マグネシウム及びカルシウムの血中濃度をポサコナゾール治療開始前及び治療中にモニタリングし、必要に応じて治療すること。

4)　CYP3A4により代謝されるミダゾラムなどのベンゾジアゼピン系薬剤

CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）とポサコナゾールを併用する際は、鎮静が延長する危険性があるため、用量調整を考慮すること。

CYP3A4により代謝されるベンゾジアゼピン系薬剤の用量調整を考慮すること（4.5項の**他剤との相互作用及びその他の相互作用**を参照すること)。

5)　ビンクリスチンの毒性

ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、痙攣発作、末梢性ニューロパチー、抗利尿ホルモン不適合分泌症候群、麻痺性イレウスなどの神経毒性及び他の重篤な副作用を引き起こすおそれがある。ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること（4.5項の**他剤との相互作用及びその他の相互作用**を参照すること)。

6)　副腎ステロイドホルモンへの影響

他のアゾール系抗真菌薬と同様に、ポサコナゾールの反復投与毒性試験でも副腎ステロイドホルモンの合成阻害に関連した影響が認められた。ラット及びイヌを用いた毒性試験では、ヒトに治療用量を投与した際に得られるのと同等以上の曝露量で副腎抑制作用が認められた。

7)　肝機能障害を有する患者への投与

4.4項の**警告及び使用上の注意**の**肝毒性**及び4.2項の**用法・用量**の**肝機能障害を有する患者への投与**を参照すること。

8)　腎機能障害を有する患者への投与

中等度又は重度（eGFR：<50 mL/min/1.73 m^2）の腎機能障害を有する患者にポサコナゾール静注用濃厚溶液を投与した場合、基剤である SBECD が蓄積するおそれがある。中等度又は重度（eGFR：<50 mL/min/1.73 m^2）の腎機能障害を有する患者では、患者の有益性及び危険性を考慮して使用が正当化されない限り、ポサコナゾール静注用濃厚溶液の投与を避けること。腎機能障害を有する患者では、血清クレアチニン値を慎重にモニタリングし、上昇が認められた場合にはポサコナゾール経口懸濁液への切り替えを考慮すること。

曝露量にばらつきが認められるため、重度の腎機能障害（eGFR：<20 mL/min/1.73 m^2）を有する患者に投与する場合には、ブレイクスルー真菌感染の有無を注意深く観察すること（5.2項

の**薬物動態的特徴**及び4.2項の**用法・用量**を参照すること）。

ポサコナゾール静注用濃厚溶液を用いた腎機能障害を有する患者での試験は実施していない。

軽度及び中等度の腎機能障害を有する患者（18例、eGFR：≥20 mL/min/1.73 m^2）を対象とするポサコナゾール経口懸濁液400 mg の単回投与試験の結果、ポサコナゾールの薬物動態への影響は認められなかったため、用量調整は不要である。重度の腎機能障害を有する患者（6例、eGFR：<20 mL/min/1.73 m^2）では、他の腎機能障害を有する患者での曝露量（40% CV）と比べてポサコナゾールの曝露量に大きなばらつき（96% CV）が認められた。しかし、ポサコナゾールは腎排泄に大きくは依存せず、重度の腎機能障害はポサコナゾールの薬物動態に影響を及ぼさないと考えられる。なお、ポサコナゾールは血液透析で除去されない。

9)　高齢者への投与

ポサコナゾール静注用濃厚溶液を投与した279例中52例（19%）が65歳を超えていた。ポサコナゾール静注用濃厚溶液の薬物動態は、若年被験者と高齢被験者で同様であった。全般的に高齢患者と若年患者で安全性に違いは認められず、また母集団薬物動態モデルにおいて年齢は有意な共変量ではなかったため、高齢患者に対する用量調整の推奨はない。

10)　小児への投与

［5.2項の**薬物動態的特徴**の**特別な背景を持つ患者における薬物動態**の**小児（18歳未満）**を参照すること］。18歳未満の小児患者に対する安全性及び有効性は確立されていない。

ポサコナゾール静注用濃厚溶液は、非臨床の安全性上の懸念があるため、小児に投与してはならない（5.3項の**非臨床安全性データ**の**非臨床における安全性**を参照すること）。

11)　臨床検査への影響

［4.8項の**有害事象（意図しない反応）**の**臨床検査値**を参照すること］。

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4. 5　他剤との相互作用やその他の相互作用

表 1.6-30　　薬物相互作用の概要（原文 6 ページ、Table 番号なし）

禁忌	治療上の有益性が危険性を上回る場合を除き、併用を避ける	他剤を用量調整する、又は有害事象をモニタリング	用量調整の必要なし
・ エルゴタミン ・ ジヒドロエルゴタミン ・ テルフェナジン ・ アステミゾール ・ シサプリド ・ ピモジド ・ キニジン ・ Halofantrine ・ 主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤	・ リファブチン ・ フェニトイン ・ シメチジン ・ エファビレンツ ・ ビンカアルカロイド	・ リファブチン ・ シクロスポリン ・ タクロリムス ・ シロリムス ・ ミダゾラム ・ アタザナビル／リトナビル ・ ホスアンプレナビル ・ CYP3A4により代謝されるカルシウムチャネル遮断薬 ・ スルホニル尿素薬 ・ ジゴキシン	・ 制酸剤 ・ ジドブジン ・ リトナビル ・ ラミブジン ・ インジナビル ・ Glipizide

薬物相互作用試験の大半は、健康被験者にポサコナゾール経口懸濁液400 mg を1日2回食事又は栄養補助剤とともに反復投与して実施したことに留意すること。ポサコナゾールの吸収に影響を及ぼす薬剤（胃内 pH 又は胃運動に影響を及ぼす薬剤）を除き、ポサコナゾール経口懸濁液で起こる薬物相互作用はポサコナゾール静注用濃厚溶液でも同様に起こると考えられる。詳細な情報は以下を参照のこと。

1)　他剤のポサコナゾールへの影響

ポサコナゾールはウリジン5'-二リン酸-グルクロン酸転移酵素（第Ⅱ相代謝酵素）により代謝され、排出トランスポーターである P-糖蛋白質（P-gp）の基質となる。したがって、これらの消失過程を阻害又は誘導する薬剤により、血漿中ポサコナゾール濃度が影響を受ける可能性がある。

(1)　リファブチン

リファブチン（300 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ43%及び49%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとリファブチンとの併用は避けること。

(2)　フェニトイン

フェニトイン（200 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ41%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとフェニトインとの併用は避けること。

(3)　シメチジン

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シメチジン（400 mg 1日2回）により、ポサコナゾール（200 mg 1日1回）の C_{max} 及び AUC は、それぞれ39%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとシメチジンとの併用は避けること。胃酸を抑制する可能性があるその他の H_2受容体拮抗薬及びプロトンポンプ阻害薬の影響は検討されていない。バイオアベイラビリティが低下するおそれがあるため、ポサコナゾールと H_2受容体拮抗薬又はプロトンポンプ阻害薬との併用は、可能な限り避けること。

(4) 制酸剤

制酸剤（25.4ミリ当量/5 mL の酸中和能に相当する液体の制酸剤）20 mL 単回投与はポサコナゾールの C_{max} 及び AUC に臨床的に意義のある影響を及ぼさなかった。したがって、ポサコナゾールの用量調整は不要である。

(5) 胃運動に影響を及ぼす薬剤

経口のポサコナゾールをメトクロプラミドと併用したところ、ポサコナゾールの薬物動態に臨床的に意義のある影響は認められなかった。したがって、メトクロプラミドと併用する際の用量調整は不要である。

(6) Glipizide

Glipizide（10 mg 単回投与）によるポサコナゾールの C_{max} 及び AUC への臨床的に意義のある影響は認められなかった。したがって、ポサコナゾールの用量調整は不要である。

(7) リトナビル

リトナビル（600 mg 1日2回）によるポサコナゾールの C_{max} 及び AUC への臨床的に意義のある影響は認められなかった。したがって、ポサコナゾールの用量調整は不要である。

(8) エファビレンツ

エファビレンツ（400 mg 1日1回）により、ポサコナゾールの C_{max} 及び AUC は、それぞれ45%及び50%低下した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとエファビレンツとの併用は避けること。

(9) ホスアンプレナビル

ホスアンプレナビルとポサコナゾールの併用により、ポサコナゾールの血漿中濃度が低下する可能性がある。ホスアンプレナビルとポサコナゾールの併用が必要な場合は、ブレイクスルー真菌感染の有無を注意深く観察することを推奨する。健康被験者20例を対象にした試験では、ホスアンプレナビルの反復投与（700 mg 1日2回10日間）により、ポサコナゾール（初日に200 mg を1日1回、2日目に200 mg を1日2回、以降400 mg を1日2回8日間）の C_{max} 及び AUC は、それぞれ21%及び23%低下した。ポサコナゾール単独をホスアンプレ

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ナビル併用と比較した際のポサコナゾールの C_{max} 及び AUC の幾何平均比は、それぞれ0.79（0.71～0.89）及び0.77（0.68～0.87）であった。

2)　ポサコナゾールの他剤への影響

ポサコナゾールの CYP 酵素系による代謝量は臨床的に意義のあるものではない。しかし、ポサコナゾールは CYP3A4の阻害剤となるため、CYP3A4により代謝される薬剤をポサコナゾールと併用した場合は、併用薬の血漿中濃度が増加する可能性がある。

(1)　テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールとの併用により、CYP3A4により代謝される特定の薬剤（テルフェナジン、アステミゾール、シサプリド、ピモジド及びキニジン等）の血漿中濃度が増加し、重篤な又は生命を脅かす有害事象（QT 延長及びまれにトルサード ド ポアント）を引き起こす可能性がある。したがって、これらの薬剤とポサコナゾールの併用は禁忌である（4.3項の**禁忌**を参照すること）。

(2)　麦角アルカロイド

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールとの併用により麦角アルカロイド（エルゴタミン及びジヒドロエルゴタミン）の血漿中濃度が増加し、麦角中毒を引き起こすことがある。麦角アルカロイドとポサコナゾールの併用は禁忌である（4.3項の**禁忌**を参照すること）。

(3)　ビンカアルカロイド

ビンカアルカロイドの大半（例：ビンクリスチン及びビンブラスチン）は CYP3A4の基質である。ポサコナゾールを含むアゾール系抗真菌薬とビンクリスチンの併用は、重篤な有害事象を引き起こすおそれがあることが知られている（4.4項の**警告及び使用上の注意**を参照すること）。ポサコナゾールとの併用によりビンカアルカロイドの血漿中濃度が増加し、神経毒性及び他の重篤な有害事象が発現する可能性がある。このため、ビンクリスチンなどのビンカアルカロイドを投与中の患者では、他の抗真菌薬を使用できない場合に限り、ポサコナゾールを含むアゾール系抗真菌薬を使用すること。

(4)　シクロスポリン

シクロスポリンの安定した用量を処方されていた心臓移植患者にポサコナゾール200 mg を1日1回反復投与した際、減量を必要とするシクロスポリンの血中濃度の増加が引き起こされた。有効性評価試験では、シクロスポリンの血中濃度の増加により腎毒性などの重篤な有害事象発現に至った複数症例及び白質脳症による死亡が1例報告された。既にシクロスポリンを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、シクロスポリンの用量を減量すること（例：現行用量の約3/4）。また、ポサコナゾ

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ールの併用期間中及び中止する際はシクロスポリンの血中濃度を注意深くモニタリングし、必要に応じてシクロスポリンの用量を調整すること。

(5) タクロリムス

ポサコナゾールとの併用によりタクロリムス（0.05 mg/kg 単回投与）の C_{max} 及び AUC は、それぞれ121%及び358%増加した。有効性評価試験では、入院又はポサコナゾールの投与中止に至った臨床的に意義のある薬物相互作用が報告された。既にタクロリムスを処方されている患者に対し、新たにポサコナゾールによる治療を開始する際は、タクロリムスの用量を減量すること（例：現行用量の約1/3）。また、ポサコナゾールの併用期間中及び中止する際はタクロリムスの血中濃度を注意深くモニタリングし、必要に応じてタクロリムスの用量を調整すること。

(6) シロリムス

健康被験者にポサコナゾール400 mg を1日2回16日間反復経口投与した際、シロリムス（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均6.7倍及び8.9倍に増加した。既にシロリムスを処方されている患者に対し､新たにポサコナゾールによる治療を開始する際は、シロリムスの用量を減量し（例：現行用量の約1/10）、シロリムスの全血中トラフ濃度を頻回にモニタリングすること。ポサコナゾールの開始時、併用中及び中止時にシロリムスの血中濃度を測定し、シロリムスの用量を適切に調整すること。

(7) リファブチン

ポサコナゾールとの併用により、リファブチンの C_{max} 及び AUC は、それぞれ31%及び72%増加した。治療上の有益性が危険性を上回る場合を除き、ポサコナゾールとリファブチンとの併用は避けること。これらの薬剤を併用する場合は、全血球数及びリファブチンの血中濃度の増加に起因する副作用（例：ぶどう膜炎）を注意深くモニタリングすることを推奨する。

(8) CYP3A4により代謝されるミダゾラムなどのベンゾジアゼピン系薬剤

健康被験者を対象とした試験では、ポサコナゾール経口懸濁液（200 mg 1日1回10日間）との併用により、ミダゾラム静注時（0.05 mg/kg）の曝露量（AUC）が83%増加した。健康被験者を対象とした他の試験では、ポサコナゾール経口懸濁液の反復経口投与（200 mg 1日2回7日間）との併用により、ミダゾラム静注時（0.4 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均1.3倍及び4.6倍（範囲：1.7～6.4倍）に増加した。ポサコナゾール経口懸濁液400 mg 1日2回7日間の併用投与では、ミダゾラム静注時の C_{max} 及び AUC は、それぞれ1.6倍及び6.2倍（範囲：1.6～7.6倍）に増加した。両投与量のポサコナゾールとの併用により、ミダゾラム経口投与時（2 mg 単回投与）の C_{max} 及び AUC は、それぞれ2.2倍及び4.5倍に増加した。さらに、ポサコナゾール経口懸濁液の投与（200 mg 又は400 mg）により、ポサコナゾールの併用期間中にミダゾラムの終末相 $t_{1/2}$の平均が約3～4時間から8～10

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時間に延長した。

CYP3A4により代謝されるベンゾジアゼピン系薬剤（例：ミダゾラム、トリアゾラム、アルプラゾラム）とポサコナゾールを併用する際は、鎮静が延長する危険性があるため、用量調整を考慮すること（4.4項の**警告及び使用上の注意**を参照すること）。

(9) ジドブジン、ラミブジン、リトナビル及びインジナビル

ジドブジン（300 mg 1日2回又は200 mg 8時間に1回）、ラミブジン（150 mg 1日2回）、リトナビル（600 mg 1日2回）又はインジナビル（800 mg 8時間に1回）を安定した用量で投与中の HIV 感染患者において、ポサコナゾールはこれらの薬剤の C_{max} 及び AUC に臨床的に意義のある影響を及ぼさなかった。ポサコナゾールの併用によりリトナビルの曝露量は30%増加したが、臨床的に意義はないと考えられた。

(10) 主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤

ポサコナゾールの反復経口投与（50、100及び200 mg 1日1回13日間）により、シンバスタチン（40 mg 単回投与）の C_{max} 及び AUC は、それぞれ平均7.4～11.4倍及び5.7～10.6倍に増加した。スタチン系薬剤の血漿中濃度の増加は横紋筋融解症を引き起こすおそれがある。したがって、主に CYP3A4により代謝される HMG-CoA 還元酵素阻害剤とポサコナゾールとの併用は禁忌である。

CYP3A4により代謝されない HMG-CoA 還元酵素阻害剤との薬物相互作用は検討されていないが、臨床推奨用量投与時のポサコナゾールの血中濃度は CYP3A4以外の CYP 分子種を阻害しないことから、CYP3A4により代謝されない HMG-CoA 還元酵素阻害剤との臨床的に意義のある薬物相互作用は起こらないと考えられる。

(11) CYP3A4により代謝されるカルシウムチャネル遮断薬

In vitro 試験及び *in vivo* 試験では検討されていないが、ポサコナゾールの併用期間中はカルシウムチャネル遮断薬に関連する副作用及び毒性を頻回にモニタリングすることを推奨する。ポサコナゾールと併用する場合、必要に応じてカルシウムチャネル遮断薬の用量を調整すること。

(12) ジゴキシン

ジゴキシンとポサコナゾールの併用により、ジゴキシンの血漿中濃度が増加することが報告されている。このため、ポサコナゾールによる治療を開始又は中止する際は、ジゴキシンの血中濃度をモニタリングする必要がある。

(13) スルホニル尿素薬

Glipizide をポサコナゾールと併用した際、一部の健康被験者でグルコースの血中濃度が低下した。糖尿病患者ではグルコースの血中濃度のモニタリングを推奨する。

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(14) HIV プロテアーゼ阻害剤

HIV プロテアーゼ阻害剤は CYP3A4の基質であるため、ポサコナゾールとの併用によりこれらの HIV プロテアーゼ阻害剤の血漿中濃度の増加が予想される。健康被験者にポサコナゾールを反復経口投与（400 mg 1日2回7日間）した際、アタザナビル（300 mg 1日1回7日間）の C_{max} 及び AUC は、それぞれ平均2.6倍及び3.7倍に増加した。リトナビルによるブースト療法下（アタザナビル300 mg 及びリトナビル100 mg の1日1回7日間併用）では、ポサコナゾール反復経口投与（400 mg 1日2回7日間）によるアタザナビルの C_{max} 及び AUC の増加はそれぞれ平均1.5倍及び2.5倍であり、リトナビルを併用しない場合と比較して増加の程度は小さかった。したがって、ポサコナゾールの併用期間中は、CYP3A4の基質である HIV プロテアーゼ阻害剤に関連する副作用及び毒性を頻回にモニタリングすることを推奨する。

(15) ホスアンプレナビル

ホスアンプレナビルをリトナビルと併用した際のホスアンプレナビルの血中濃度に対するポサコナゾールの影響は不明である。健康被験者20例を対象にした試験では、ポサコナゾール（初日に200 mg を1日1回、2日目に200 mg を1日2回、以降400 mg を1日2回8日間）をホスアンプレナビル（700 mg 1日2回10日間）と併用した際、アンプレナビルの C_{max} 及び AUC は、ホスアンプレナビルとリトナビルの併用時と比べてそれぞれ36%及び65%低下した。ホスアンプレナビルとリトナビルの併用時に対する、ホスアンプレナビルとポサコナゾール併用時のアンプレナビルの C_{max} 及び AUC の幾何平均比は、それぞれ0.64（0.55～0.76）及び0.35（0.32～0.39）であった。

4．6　生殖能、妊娠及び授乳

1)　生殖能への影響

雄ラットにポサコナゾールを最高180 mg/kg/日（ヒトに300 mg を静脈内投与したときに得られる曝露量の2.8倍に相当）まで経口投与したところ、生殖能への影響は認められなかった。雌ラットにポサコナゾールを最高45 mg/kg/日（患者に300 mg を静脈内投与したときに得られる曝露量の3.4倍に相当）まで交配前2週間経口投与したところ、生殖能への影響は認められなかったが、4週間投与した雌ラットには発情周期異常が認められた。

2)　妊婦への投与

胎児危険度分類 B3：妊婦を対象とした適切な試験は実施されていない。ポサコナゾール経口懸濁液を投与された女性被験者で計3件の妊娠が報告されている。2件は中絶が選択され、胎児に対する検査の報告はなかった。残り1件は、同種 HSCT を受けた患者がポサコナゾール経口懸濁液200 mg の1日3回16週間の予防投与を完了し、約1ヵ月後の追跡調査のため来院した際に診断された妊娠であった。この妊婦は帝王切開により健康な男児を満期出産した。

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ラットに経口投与した試験では、ヒトでの臨床推奨用量で予想される曝露量よりも低い曝露量において、着床後死亡、骨格変異増加、催奇形性（頭蓋顔面奇形）、妊娠期間延長、難産及び出生後生存率の低下などの生殖毒性が示された。ウサギでは、ヒトに治療用量のポサコナゾール経口懸濁液を投与したときよりも高い血漿中曝露量において、着床後死亡増加及び骨格変異増加が認められた。

母親への治療上の有益性が胎児への危険性を明らかに上回る場合を除き、ポサコナゾールを妊娠中に投与してはならない。妊娠可能な女性には、投与期間中及び投与完了後2週間以上は有効な避妊法を使用するよう指導しなければならない。

3)　授乳婦への投与

ポサコナゾールは授乳期ラットの乳汁中に移行する。ヒト乳汁中へのポサコナゾールの移行は検討していない。ポサコナゾールを服用中の女性は授乳してはならない。

4．7　運転及び機械操作に対する影響

ポサコナゾール使用時に、運転や機械操作に影響する可能性がある潜在的な有害反応（浮動性めまい、傾眠等）がみられていることから、注意が必要である。

4．8　有害事象（意図しない反応）

1)　ポサコナゾール静注用濃厚溶液

ポサコナゾール静注用濃厚溶液の臨床試験で報告された有害事象の種類及び発現割合は、ポサコナゾール経口懸濁液で報告されたものと概して同様であった。

健康被験者を対象とした初期の試験では、末梢静脈カテーテルを通じて30分間かけてポサコナゾール静注用濃厚溶液を単回注入した場合の忍容性は良好であった。しかし、末梢静脈カテーテルを介したポサコナゾール静注用濃厚溶液の反復投与により血栓性静脈炎が認められた（発現割合：60%）。そのため、その後の試験ではポサコナゾール静注用濃厚溶液は中心静脈カテーテルを介して投与された。中心静脈カテーテルを直ちに使用できない場合は、単回であれば30分間かけて末梢静脈カテーテルを通じて投与してもよいこととされた。

臨床試験で患者268例を対象にポサコナゾール静注用濃厚溶液の安全性を評価した。患者は真菌症予防を目的としたポサコナゾール静注用濃厚溶液の薬物動態及び安全性評価の非対照試験に組み入れられた（P05520試験）。患者は血液悪性腫瘍、化学療法後の好中球減少症、移植片対宿主病、HSCT 後などの基礎疾患を伴う免疫不全状態にあった。この患者集団では、男性55%、平均年齢51歳（範囲：18～82歳、65歳以上：19%）、白人95%、ヒスパニック系8%であった。10例にポサコナゾール静注用濃厚溶液 200 mg を単回投与、21例に200 mg/日を14日間（中央値）、237例に300 mg/日を9日間（中央値）投与した。反復投与コホートの各患者は、初日に1日2回投与した。ポサコナゾールを合計28日間投与するため、各コホートでポサコナゾールの静脈内投

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与後、ポサコナゾール経口懸濁液を投与した。臨床試験では、14日間を超えて推奨用量のポサコナゾール静注用濃厚溶液を投与した際の安全性及び有効性は評価されていない。

ポサコナゾール静注用濃厚溶液の試験において、ポサコナゾール静注用濃厚溶液300 mg/日を投与した患者に認められた発現割合10%以上の治療期の有害事象の発現例数を[表 1.6-31]に示す。

表 1.6-31　　ポサコナゾール静注用濃厚溶液の予防投与試験（P05520 試験）
300 mg/日投与患者における発現割合 10%以上の有害事象の発現例数（%）（原文 Table 3）

器官別大分類 基本語	ポサコナゾール 静注用濃厚溶液投与期 n=237 (%)†		ポサコナゾール静注用濃厚溶液投与期 又はそれに続く経口懸濁液投与期 n=237 (%)‡	
有害事象が認められた患者	220	(93)	235	(99)
血液およびリンパ系障害				
貧血	16	(7)	23	(10)
発熱性好中球減少症	44	(19)	54	(23)
血小板減少症	17	(7)	25	(11)
胃腸障害				
上腹部痛	15	(6)	25	(11)
腹痛	30	(13)	41	(17)
便秘	18	(8)	31	(13)
下痢	75	(32)	93	(39)
悪心	46	(19)	70	(30)
嘔吐	29	(12)	45	(19)
一般・全身障害および投与部位の状態				
疲労	19	(8)	24	(10)
悪寒	28	(12)	38	(16)
粘膜の炎症	37	(16)	44	(19)
末梢性浮腫	28	(12)	35	(15)
発熱	49	(21)	73	(31)
代謝および栄養障害				
食欲減退	23	(10)	29	(12)
低カリウム血症	51	(22)	67	(28)
低マグネシウム血症	25	(11)	30	(13)
神経系障害				
頭痛	33	(14)	49	(21)
呼吸器、胸郭および縦隔障害				
咳嗽	21	(9)	31	(13)
呼吸困難	16	(7)	24	(10)
鼻出血	34	(14)	40	(17)
皮膚および皮下組織障害				
点状出血	20	(8)	24	(10)
発疹	35	(15)	56	(24)
血管障害				
高血圧	20	(8)	26	(11)

† 本試験のポサコナゾール静脈内投与期間中に患者に認められた有害事象
‡ 本試験のポサコナゾール投与期間中（最長28日間）にいずれかの時点で患者に認められた有害事象

ポサコナゾール静注用濃厚溶液300 mg 1日1回の静脈内投与期間中に認められた有害事象で発現割合が最も高い（>30%）事象は、下痢（32%）であった。

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ポサコナゾール静注用濃厚溶液300 mg 1日1回で投与中止に至った有害事象で発現割合が最も高い（>1%）事象は、急性骨髄性白血病（AML）（1%）であった。

2)　ポサコナゾール経口懸濁液

ポサコナゾール経口懸濁液を投与した2,400例で認められた副作用を[表 1.6-32]に示す。172例が6ヵ月以上、58例が12ヵ月以上の投与を受けた。

健康被験者と患者の全集団で認められた副作用で発現割合が高い事象は、悪心（6%）及び頭痛（6%）であった。

表 1.6-32　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 4）

よくみられる（>1/100、<1/10）、あまりみられない（>1/1,000、<1/100）、まれな（>1/10,000、<1/1,000）

感染症および寄生虫症	
あまりみられない： まれな：	口腔カンジダ症、副鼻腔炎 カテーテル関連感染、疱疹性以外の口唇ヘルペス、食道カンジダ症、肺炎、上気道感染、尿路感染
血液およびリンパ系障害	
よくみられる： あまりみられない： まれな：	好中球減少症 貧血、血小板減少症、白血球減少症、好酸球増加症、リンパ節症 血液ガス異常、溶血性尿毒症症候群、好中球増加症、汎血球減少症、凝固障害、出血 NOS、血小板数増加、プロトロンビン減少、プロトロンビン時間延長、紫斑、血栓性血小板減少性紫斑病
免疫系障害	
あまりみられない： まれな：	アレルギー反応 過敏症反応、スティーヴンス・ジョンソン症候群
内分泌障害	
まれな：	副腎機能不全、ゴナドトロピン減少
代謝および栄養障害	
よくみられる： あまりみられない： まれな：	食欲不振、電解質失調 高血糖、高トリグリセリド血症、高尿酸血症、体重減少、LDH 増加、脱水 アミラーゼ増加、高コレステロール血症、高脂血症、高蛋白血症、低アルブミン血症、リパーゼ増加、代謝性アシドーシス、腎尿細管性アシドーシス、ビタミン K 欠乏、体重増加
精神障害	
あまりみられない： まれな：	精神状態変化、不安、錯乱、不眠症 健忘、うつ病、異常な夢、情動不安定、リビドー減退、魔夢、精神病

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表 1.6-32　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 4）（続き）

神経系障害	
よくみられる：	浮動性めまい、頭痛、錯感覚、傾眠
あまりみられない：	ニューロパチー、感覚鈍麻、痙攣、振戦
まれな：	末梢性ニューロパチー、反射消失、運動失調、認知障害、譫妄、発声障害、ジストニア、脳症、不全片麻痺、運動過多、反射亢進、反射減弱、筋緊張低下、集中力障害、記憶障害、髄膜症、単神経炎、下肢静止不能症候群、坐骨神経痛、失神
眼障害	
あまりみられない：	結膜炎、霧視
まれな：	眼痛、眼乾燥、眼窩周囲浮腫、複視、羞明、暗点
耳および迷路障害	
あまりみられない：	耳痛、回転性めまい
まれな：	聴力障害、耳鳴
心臓障害	
あまりみられない：	ECG 異常、QT/QTc 延長、心房粗動、心房細動、脚ブロック、頻脈、期外収縮、動悸、心室肥大
まれな：	徐脈、心不全、心肺停止、突然死、心室性頻脈、大動脈弁硬化症、心拡大、駆出率減少、僧帽弁疾患 NOS、心筋梗塞、上室性頻脈、心房性期外収縮、心室性期外収縮、AV ブロック、トルサード ド ポアント
血管障害	
あまりみられない：	潮紅、ほてり、高血圧、低血圧
まれな：	アテローム性動脈硬化症、脳血管発作、深部静脈血栓症 NOS、肺塞栓症、虚血、血腫
呼吸器、胸郭および縦隔障害	
あまりみられない：	胸痛、咳嗽、呼吸困難、鼻出血、咽頭炎、鼻閉
まれな：	無気肺、咽喉乾燥、肺高血圧症、間質性肺炎、鼻刺激感、肺臓炎、後鼻漏、肺浸潤、ラ音、鼻炎、鼻漏
胃腸障害	
よくみられる：	腹痛、下痢、消化不良、鼓腸、口内乾燥、悪心、嘔吐
あまりみられない：	味覚倒錯、便秘、ゆるい便、腹部膨満、嚥下障害、腹水、おくび、口渇、胃炎、胃食道逆流、粘膜炎 NOS、食道炎、膵炎、舌変色
まれな：	胃腸管出血、イレウス、腹部圧痛、口唇炎、血性下痢、食道潰瘍形成、出血性胃炎、嚥下痛、膵酵素 NOS 増加、肛門周囲痛、レッチング、アフタ性口内炎、しぶり、メレナ、歯肉炎、舌炎
肝胆道系障害	
よくみられる：	肝機能検査値（AST、ALT、ALP、GGT、ビリルビン等）上昇
あまりみられない：	肝炎、肝細胞損傷、肝腫大、黄疸
まれな：	固定姿勢保持困難、胆汁うっ滞、肝不全、胆汁うっ滞性肝炎、肝脾腫大、肝圧痛、脾腫
皮膚および皮下組織障害	
よくみられる：	発疹
あまりみられない：	脱毛症、皮膚乾燥、斑状丘疹状皮疹、蕁麻疹、せつ腫症、ざ瘡、口腔内潰瘍形成、そう痒症、そう痒性皮疹
まれな：	口内炎、皮膚炎、紅斑、紅斑性皮疹、毛孔性皮疹、斑状皮疹、寝汗、脂漏、皮膚小結節、小水疱性皮疹
筋骨格系および結合組織障害	
あまりみられない：	筋肉痛、関節痛、背部痛、筋骨格痛、側腹部痛、筋力低下
まれな：	骨痛、胸壁痛、筋膜炎、頚部硬直、四肢痙攣、筋痙攣

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表 1.6-32　　ポサコナゾール経口懸濁液投与例における
器官別大分類及び発現割合別の副作用（2,400 例）（原文 Table 4）（続き）

腎および尿路障害	
あまりみられない：	アルブミン尿、排尿回数変化、排尿困難、血中クレアチニン増加、急性腎不全、腎不全、血尿、腎機能障害、夜間頻尿
まれな：	BUN 増加、間質性腎炎、排尿異常、腎結石、尿路閉塞 NOS
生殖系および乳房障害	
あまりみられない：	月経障害
まれな：	白帯下、乳房痛
一般・全身障害および投与部位の状態	
よくみられる：	無力症、疲労、発熱
あまりみられない：	多汗、疼痛、悪寒、倦怠感、脱力、浮腫、変色歯
まれな：	顔面浮腫、舌浮腫
臨床検査	
あまりみられない：	薬物濃度変化
傷害、中毒および処置合併症	
あまりみられない：	薬物毒性 NOS
まれな：	斑状出血

NOS：他に特定されない、LDH：乳酸脱水素酵素、ECG：心電図、QTc：心拍数補正 QT 間隔、AV：房室、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、ALP：アルカリホスファターゼ、GGT：γ-グルタミルトランスフェラーゼ、BUN：尿素窒素

重篤な副作用は、難治性侵襲性真菌症患者の併合集団の8%（35/428例）で認められた。個々の重篤な副作用の大半は発現割合が1%未満であり、大部分が侵襲性真菌症を発症する素因となる重篤な基礎疾患を反映する事象であった。発現割合が1%（3又は4例）の重篤な副作用は、他剤の薬物濃度変化、肝酵素上昇、悪心、発疹及び嘔吐であった。一方、予防のためポサコナゾール経口懸濁液を投与された患者605例でみられた重篤な副作用は、ビリルビン血症、肝酵素上昇、肝細胞損傷、悪心及び嘔吐（各1%）などであった。

ポサコナゾール経口懸濁液での臨床試験中にみられた、まれで医学的に意味のある副作用は、副腎機能不全、膵炎、アレルギー又は過敏症反応などであった。

一部のアゾール系抗真菌薬は、心電図の QT 延長を引き起こすことが知られている。ポサコナゾール経口懸濁液を投与された健康被験者173例において同一時刻に心電図を記録した併合解析では、QT 間隔を延長させる可能性は示されなかった。なお、ポサコナゾール経口懸濁液を投与された患者でのトルサード ド ポアントの報告はまれであった。

さらに、主に移植後の拒絶反応又は移植片対宿主病の管理のためシクロスポリン又はタクロリムスを併用している患者に、溶血性尿毒症症候群及び血栓性血小板減少性紫斑病がまれに認められた。

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表 1.6-33　　ポサコナゾール経口懸濁液を投与された侵襲性真菌症患者における発現割合 1%以上の副作用（程度は治験担当医師判定に基づく）（原文 Table 5）

事象名	すべての副作用	軽度／中等度のすべての副作用	重度／生命を脅かすすべての副作用
	n=330 発現例数（%）	n=330 発現例数（%）	n=330 発現例数（%）
一般的全身障害			
食欲不振	8 (2)	8 (2)	0
無力症	4 (1)	4 (1)	0
胸痛	2 (1)	2 (1)	0
浮動性めまい	7 (2)	6 (2)	1 (<1)
薬物濃度変化	7 (2)	4 (1)	3 (1)
疲労	7 (2)	6 (2)	1 (<1)
発熱	3 (1)	3 (1)	0
頭痛	15 (5)	13 (4)	2 (1)
脱力	2 (1)	2 (1)	0
心・血管障害（一般）			
心肺停止	2 (1)	0	2 (1)
心室肥大	2 (1)	1 (<1)	1 (<1)
中枢・末梢神経系障害			
錯乱	3 (1)	3 (1)	0
痙攣	2 (1)	0	2 (1)
反射亢進	2 (1)	2 (1)	0
感覚鈍麻	2 (1)	2 (1)	0
精神状態変化	2 (1)	2 (1)	0
錯感覚	6 (2)	6 (2)	0
傾眠	3 (1)	3 (1)	0
振戦	2 (1)	2 (1)	0
血液およびリンパ系障害	6 (2)	4 (1)	2 (1)
貧血	4 (1)	3 (1)	1 (<1)
眼障害	4 (1)	3 (1)	1 (<1)
霧視	2 (1)	2 (1)	0
生殖系および乳房障害			
乳房痛	1 (<1)	1 (<1)	0
月経障害（女性のみに基づく）	2 (2)	2 (2)	0
消化管障害			
腹部膨満	2 (1)	2 (1)	0
腹痛	16 (5)	13 (4)	3 (1)
便秘	2 (1)	2 (1)	0
下痢	11 (3)	10 (3)	1 (<1)
消化不良	2 (1)	2 (1)	0
鼓腸	3 (1)	3 (1)	0
口内乾燥	5 (2)	5 (2)	0
悪心	31 (9)	2 (1)	29 (9)
嘔吐	19 (6)	18 (5)	1 (<1)
心拍数・心リズム障害			
心房粗動	2 (1)	1 (<1)	1 (<1)
特異的 ECG 異常	2 (1)	2 (1)	0
期外収縮	2 (1)	1 (<1)	1 (<1)
心房細動	3 (1)	2 (1)	1 (<1)
QT/QTc 延長	6 (2)	6 (2)	0
頻脈	2 (1)	2 (1)	0
上室性頻脈	2 (1)	1 (<1)	1 (<1)
傷害及び中毒			
薬物毒性 NOS	2 (1)	0	2 (1)
肝臓・胆管系障害			
ビリルビン血症	4 (1)	3 (1)	1 (<1)

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表 1.6-33　　ポサコナゾール経口懸濁液を投与された侵襲性真菌症患者における発現割合 1%以上の副作用（程度は治験担当医師判定に基づく）（原文 Table 5）（続き）

事象名	すべての副作用 n=330 発現例数（%）	軽度／中等度のすべての副作用 n=330 発現例数（%）	重度／生命を脅かすすべての副作用 n=330 発現例数（%）
γ-GT 増加	2 (1)	0	2 (2)
肝酵素上昇	7 (2)	6 (2)	1 (<1)
肝機能異常	2 (1)	2 (1)	0
黄疸	2 (1)	1 (<1)	1 (<1)
AST 増加	9 (3)	6 (2)	3 (1)
ALT 増加	11 (3)	9 (3)	2 (1)
代謝・栄養障害			
アルカリホスファターゼ増加	6 (2)	5 (2)	1 (<1)
口渇	2 (1)	2 (1)	0
筋・骨格系障害			
筋骨格痛	2 (1)	2 (1)	0
血小板・出血凝血障害			
血小板減少症	2 (1)	2 (1)	0
腎および尿路障害			
血中クレアチニン減少	5 (2)	4 (2)	1 (<1)
夜間頻尿	2 (1)	2 (1)	0
腎不全	2 (1)	1 (<1)	1 (<1)
急性腎不全	2 (1)	0	2 (1)
皮膚および皮下組織障害			
脱毛症	4 (1)	4 (1)	0
皮膚乾燥	3 (1)	3 (1)	0
そう痒症	3 (1)	3 (1)	0
発疹	9 (3)	7 (2)	2 (1)
斑状丘疹状皮疹	4 (1)	3 (1)	1 (<1)
小水疱性皮疹	2 (1)	2 (1)	0

ECG：心電図、QTc：心拍数補正 QT 間隔、NOS：他に特定されない、GT：グルタミルトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ

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表 1.6-34　　ポサコナゾール経口懸濁液を投与された口腔咽頭カンジダ症患者における発現割合 2%以上の副作用（すべてのグレード）（原文 Table 6）

事象名	患者数（%）		
	OPC 比較試験データの併合		難治性 OPC 試験データの併合
	ポサコナゾール経口懸濁液 n=557	フルコナゾール n=262	ポサコナゾール経口懸濁液 n=239
有害事象が認められた患者†	150 (27)	70 (27)	135 (56)
一般的全身障害			
食欲不振	6 (1)	1 (<1)	7 (3)
無力症	4 (1)	2 (1)	6 (3)
浮動性めまい	9 (2)	5 (2)	8 (3)
疲労	8 (1)	5 (2)	7 (3)
発熱	10 (2)	1 (<1)	6 (3)
頭痛	16 (3)	5 (2)	18 (8)
中枢・末梢神経系障害			
傾眠	4 (1)	5 (2)	3 (1)
血液およびリンパ系障害			
貧血	2 (<1)	0 (0)	6 (3)
好中球減少症	10 (2)	4 (2)	20 (8)
消化管障害			
腹痛	10 (2)	8 (3)	12 (5)
下痢	19 (3)	13 (5)	26 (11)
鼓腸	6 (1)	0 (0)	11 (5)
口内乾燥	7 (1)	6 (2)	5 (2)
悪心	27 (5)	18 (7)	20 (8)
嘔吐	20 (4)	4 (2)	16 (7)
肝臓・胆管系障害			
肝酵素上昇	1 (<1)	0 (0)	5 (2)
肝機能異常	3 (1)	4 (2)	0 (0)
代謝・栄養障害			
アルカリホスファターゼ増加	3 (1)	3 (1)	5 (2)
筋・骨格系障害			
筋肉痛	1 (<1)	0 (0)	4 (2)
血小板・出血凝血障害			
血小板減少症	3 (1)	0 (0)	4 (2)
精神障害			
不眠症	3 (1)	0 (0)	6 (3)
皮膚および皮下組織障害			
そう痒症	6 (1)	2 (1)	5 (2)
発疹	8 (1)	4 (2)	10 (4)

OPC：口腔咽頭カンジダ症
† 試験期間中に有害事象が1件以上認められた患者数。事象が複数回認められた患者がいる可能性もある。

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表 1.6-35　　CI98-316 試験及び P01899 試験
ポサコナゾール経口懸濁液又はフルコナゾールの予防投与患者における
発現割合 2%以上のすべての副作用及び重度／生命を脅かす副作用の発現例数（%）（原文 Table 7）

	ポサコナゾール 経口懸濁液 n=605		フルコナゾール n=539		イトラコナゾール n=58	
	すべての副作用	重度／生命を脅かす副作用	すべての副作用	重度／生命を脅かす副作用	すべての副作用	重度／生命を脅かす副作用
副作用が認められた患者†	209 (35)	81 (13)	186 (35)	53 (10)	30 (52)	6 (10)
消化管障害						
腹痛	13 (2)	1 (<1)	15 (3)	2 (<1)	1 (2)	0
便秘	4 (1)	0	12 (2)	0	0	0
下痢	28 (5)	4 (1)	24 (4)	1 (<1)	9 (16)	0
消化不良	8 (1)	1 (<1)	9 (2)	0	0	0
悪心	44 (7)	5 (1)	45 (8)	1 (<1)	8 (14)	0
嘔吐	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
心拍数・心リズム障害						
QT/QTc 延長	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
肝臓・胆管系障害						
ビリルビン血症	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT 増加	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
肝酵素上昇	15 (2)	11 (2)	10 (2)	3 (1)	0	0
AST 増加	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
ALT 増加	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	1 (2)
代謝・栄養障害						
低カリウム血症	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
皮膚および皮下組織障害						
発疹	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

QTc：心拍数補正 QT 間隔、GGT：γ-グルタミルトランスフェラーゼ、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ
† 試験期間中に副作用が1件以上認められた患者数。事象が複数回認められた患者がいる可能性もある。

3)　臨床検査値

侵襲性真菌症患者にポサコナゾール経口懸濁液800 mg/日を投与した（非対照）試験での臨床的に意義のある肝機能検査異常の発現割合は、ALT 及び AST［基準値上限（ULN）の3倍超］がそれぞれ11%及び10%、総ビリルビン（ULN の1.5倍超）が22%、ALP（ULN の3倍超）が14%であった。健康被験者で認められた肝酵素上昇は血漿中ポサコナゾール濃度の高値と関連しないと考えられた。患者で認められた大多数の肝機能検査異常は軽微で一過性の変化であり、投与中止に至ることはまれであった。

HIV 感染患者にポサコナゾールを最高400 mg まで投与した比較試験での臨床的に意義のある肝機能検査異常の発現割合は、ALT 及び AST（ULN の3倍超）がそれぞれ3%及び6%、総ビリルビン（ULN の1.5倍超）が3%、ALP（ULN の3倍超）が3%であった。

予防投与試験（CI98-316試験及び P01899試験）で共通毒性基準（CTC）に基づく肝機能検査値が、ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数を[表 1.6-36]に示す。

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表 1.6-36　　ポサコナゾール経口懸濁液 CI98-316 試験及び P01899 試験
肝機能検査値がベースライン時の CTC Grade 0、1 又は 2 から
Grade 3 又は 4 へ変化した患者数（原文 Table 8）

臨床検査値	変化が認められた患者数（%）†	
	ポサコナゾール経口懸濁液の試験（CI98-316試験）	
	ポサコナゾール n=301	フルコナゾール n=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
ビリルビン	24/271 (9)	20/275 (7)
ALP	9/271 (3)	8/271 (3)
	ポサコナゾール経口懸濁液の試験（P01899試験）	
	ポサコナゾール n=304	フルコナゾール／イトラコナゾール n=298
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
ビリルビン	20/290 (7)	25/285 (9)
ALP	4/281 (1)	1/276 (<1)

† ベースライン時の Grade 0、1又は2から試験期間中に Grade 3又は4へ変化した患者数。X はその定義を満たす患者数、Y はベースライン値が得られ、かつベースライン後の1時点以上で検査値が得られた患者数として、X/Y の形式でデータを示す。
CTC：共通毒性基準、AST：アスパラギン酸アミノトランスフェラーゼ、ALT：アラニンアミノトランスフェラーゼ、ALP：アルカリホスファターゼ

4)　副作用の報告

承認登録後にも本剤と因果関係が疑われる有害事象（副作用）を報告することは重要である。それにより、医薬品の有益性及び危険性のバランスを継続的に監視することができる。医療従事者は www.tga.gov.au/reporting-problems へそのような副作用を報告すること。

4. 9　過量投与

ポサコナゾール静注用濃厚溶液の過量投与は報告されていない。

臨床試験において、ポサコナゾール経口懸濁液が最高1,600 mg/日投与された被験者で発現した有害事象は、より低用量で認められたものと同様であった。また、ポサコナゾール経口懸濁液1,200 mg を1日2回3日間投与された偶発的過量投与の患者が1例報告された。治験担当医師判定による過量投与に起因する副作用は報告されなかった。

重度の血液透析依存腎機能障害を有する患者（クレアチニンクリアランス：<20 mL/min）を対象とした試験において、ポサコナゾールは血液透析で除去されなかった。そのため、血液透析はポサコナゾールを全身循環血から除去する上で有効ではないと考えられる。

過量投与の管理情報については、Poison Information Centre（オーストラリア国内 131126）に連絡すること。

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1.6.2.2　　外国の添付文書（原文）

1.6.2.2.1　　米国添付文書（原文）

2017年9月版の添付文書を添付する。

（crt-uspi-mk5592-mf-1709r039.pdf）

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NOXAFIL safely and effectively. See full prescribing information for NOXAFIL.

NOXAFIL® (posaconazole) injection, for intravenous use
NOXAFIL® (posaconazole) delayed-release tablets, for oral use
NOXAFIL® (posaconazole) oral suspension
Initial U.S. Approval: 2006

----------INDICATIONS AND USAGE----------
Noxafil is an azole antifungal agent indicated for:
injection, delayed-release tablets, and oral suspension
- prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. (1.1)

Oral suspension
- treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Noxafil delayed-release tablets and oral suspension are not interchangeable due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations. (2.3, 2.4)

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	**Injection*:** Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.1) **Delayed-Release Tablets†:** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.2) **Oral Suspension‡:** 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.3)
Oropharyngeal Candidiasis (OPC)	**Oral Suspension‡:** Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days. (2.3)
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	**Oral Suspension‡:** 400 mg (10 mL) twice a day. Duration of therapy is based on the severity of the patient's underlying disease and clinical response. (2.3)

*Noxafil injection must be administered through an in-line filter. Administer by intravenous infusion over approximately 90 minutes via a central venous line. Never give Noxafil injection as an intravenous bolus injection. (2)
†Noxafil delayed-release tablets should be taken with food. (2)
‡Noxafil oral suspension should be taken with a full meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------
- Noxafil injection: 300 mg per 16.7 mL (18 mg per mL) (3)
- Noxafil delayed-release tablet 100 mg (3)
- Noxafil oral suspension 40 mg per mL (3)

----------CONTRAINDICATIONS----------
- Do not administer to persons with known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
- Do not coadminister Noxafil with the following drugs; Noxafil increases concentrations of:
  - Sirolimus: can result in sirolimus toxicity (4.2, 7.1)
  - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and cases of TdP (4.3, 7.2)
  - HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4: can lead to rhabdomyolysis (4.4, 7.3)
  - Ergot alkaloids: can result in ergotism (4.5, 7.4)

---------- WARNINGS AND PRECAUTIONS ----------
- Calcineurin Inhibitor Toxicity: Noxafil increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: Noxafil has been shown to prolong the QTc interval and cause cases of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. Correct K^+, Mg^{++}, and Ca^{++} before starting Noxafil. (5.2)
- Hepatic Toxicity: Elevations in LFTs may occur. Discontinuation should be considered in patients who develop abnormal LFTs or monitor LFTs during treatment. (5.3)
- Noxafil injection should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. (5.4, 8.6)
- Midazolam: Noxafil can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.5, 7.5)
- Vincristine Toxicity: Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions; reserve azole antifungals, including Noxafil, for patients receiving a vinca a kaloid, including vincristine, who have no alternative antifungal treatment options. (5.6, 7.10)

---------- ADVERSE REACTIONS ----------
- Common treatment-emergent adverse reactions in studies with posaconazole are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Interaction Drug	*Interaction*
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole*	*Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)*
Other drugs metabolized by CYP3A4	*Consider dosage adjustment and monitor for adverse effects and toxicity (7.1, 7.10, 7.11)*
Digoxin	*Monitor digoxin plasma concentrations (7.12)*
Fosamprenavir, metoclopramide*	*Monitor for breakthrough fungal infections (7.6, 7.13)*
*The drug interactions with esomeprazole and metoclopramide do not apply to posaconazole tablets.	

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking in to consideration the importance of drug to the mother. (8.3)
- Severe renal impairment: Monitor closely for breakthrough fungal infections. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2017

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- 17.1 Administration
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- 17.3 Serious and Potentially Serious Adverse Reactions

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

Noxafil® injection, delayed-release tablets, and oral suspension are indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Noxafil injection is indicated in patients 18 years of age and older.

Noxafil delayed-release tablets and oral suspension are indicated in patients 13 years of age and older.

1.2 Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole

Noxafil oral suspension is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions for Noxafil Injection, Noxafil Delayed-Release Tablets and Noxafil Oral Suspension

Noxafil delayed-release tablets and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation *[see Dosage and Administration (2.3, 2.4, 2.5)]*.

Noxafil injection

- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes *[see Dosage and Administration (2.2)]*.
- If a central venous catheter is not available, Noxafil injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a single dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other intravenous treatment.
- When multiple dosing is required, the infusion should be done via a central venous line.
- Never administer Noxafil injection as an intravenous bolus injection.

Noxafil delayed-release tablets

- Swallow tablets whole. Do not divide, crush, or chew.
- Administer with food *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Noxafil oral suspension

- Administer with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal *[see Dosage and Administration (2.4)]*
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections *[see Drug Interactions (7.6, 7.7, 7.8, 7.9, 7.13)]*

Noxafil delayed-release tablets and Noxafil oral suspension

- Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections when receiving Noxafil delayed-release tablets or oral suspension.

2.2 Dosage, Preparation, Intravenous Line Compatibility and Administration of Noxafil Injection

Dosage:

Table 1: Dosage for Noxafil Injection

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Preparation:

- Equilibrate the refrigerated vial of Noxafil (posaconazole) injection to room temperature.
- To prepare the required dose, aseptically transfer one vial (16.7 mL) of Noxafil injection (containing 300 mg of posaconazole in solution) to an intravenous bag (or bottle) of a compatible admixture

diluent (as described in **Table 2**), to achieve a final concentration of posaconazole that is between 1 mg/mL and 2 mg/mL. Use of other diluents is not recommended because they may result in particulate formation.

- Noxafil injection is a single dose sterile solution without preservatives. Once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2-8°C (36-46°F). Noxafil injection is for single use only and any unused solution should be discarded.
- Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the solution of Noxafil ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.

Intravenous Line Compatibility:

A study was conducted to evaluate physical compatibility of Noxafil injection with injectable drug products and commonly used intravenous diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity. Compatible diluents and drug products are listed in **Tables 2 and 3** below. Any diluents or drug products not listed in the tables below should not be co-administered through the same intravenous line (or cannula).

- Noxafil injection can be infused at the same time through the same intravenous line (or cannula) with the following compatible diluents:

Table 2: Compatible Diluents

0.45% sodium chloride
0.9% sodium chloride
5% dextrose in water
5% dextrose and 0.45% sodium chloride
5% dextrose and 0.9% sodium chloride
5% dextrose and 20 mEq potassium chloride

- Noxafil injection can be infused at the same time through the same intravenous line (or cannula) with the following drug products prepared in 5% dextrose in water or sodium chloride 0.9%. Co-administration of drug products prepared in other diluents may result in particulate formation.

Table 3: Compatible Drugs

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulfate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Incompatible Diluents:

Noxafil injection must not be diluted with the following diluents:

Lactated Ringer's solution
5% dextrose with Lactated Ringer's solution
4.2% sodium bicarbonate

Administration:

- Noxafil injection must be administered through a 0.22 micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter.
- Administer via a central venous line, including a central venous catheter or PICC by slow infusion over approximately 90 minutes. Noxafil injection is not for bolus administration.
- If a central venous catheter is not available, Noxafil injection may be administered through a peripheral venous catheter only as a single dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other treatment.
- When multiple dosing is required, the infusion should be done via a central venous line. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes. Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions *[see Adverse Reactions (6.2)]*.

2.3 Dosage and Administration Instructions for Noxafil Delayed-Release Tablets

Dosage:

Table 4: Dosage for Noxafil Delayed-Release Tablets

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Administration Instructions for Noxafil Delayed-Release Tablets:

- Swallow tablets whole. Do not divide, crush, or chew.
- Administer Noxafil delayed-release tablets with food to enhance the oral absorption of posaconazole and optimize plasma concentrations *[see Clinical Pharmacology (12.3)].*
- Noxafil delayed-release tablets should be used only for the prophylaxis indication.
- Noxafil delayed-release tablets generally provide higher plasma drug exposures than Noxafil oral suspension under both fed and fasted conditions, and therefore is the preferred oral formulation for the prophylaxis indication.

2.4 Dosage and Administration Instructions for Noxafil Oral Suspension

Dosage:

Table 5: Dosage for Noxafil Oral Suspension

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Oropharyngeal Candidiasis	Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days.
Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

Administration Instructions for Noxafil Oral Suspension:

- Shake Noxafil oral suspension well before use. Administer with measured dosing spoon (see Figure 1) provided.

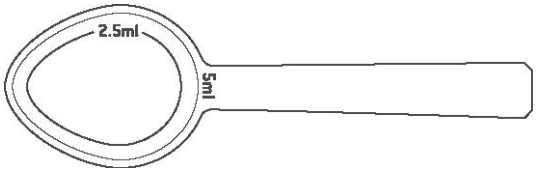


Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.

- Rinse the spoon with water after each administration and before storage.
- Administer each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal to enhance the oral absorption of Noxafil and optimize plasma concentrations *[see Clinical Pharmacology (12.3)]*.
- For patients who cannot eat a full meal, Noxafil delayed-release tablets should be used instead of Noxafil oral suspension. Noxafil delayed-release tablets should be used only for the prophylaxis indication. Noxafil delayed-release tablets provide higher plasma drug exposures than Noxafil oral suspension under fasted conditions *[See Dosage and Administration (2.5)]*.
- In patients who cannot eat a full meal and for whom Noxafil delayed-release tablets or Noxafil injection are not options, administer each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).
- For patients who cannot eat a full meal or tolerate an oral nutritional supplement or an acidic carbonated beverage and who do not have the option of taking Noxafil delayed-release tablets or Noxafil injection, an alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.

2.5 Non-Interchangeability between Noxafil Delayed-Release Tablets and Noxafil Oral Suspension

Noxafil delayed-release tablets and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations *[see Dosage and Administration (2.3, 2.4)]*.

2.6 Dosage Adjustments in Patients with Renal Impairment

The pharmacokinetics of Noxafil oral suspension and delayed-release tablets are not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

- Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection.
- In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min), receiving the Noxafil injection, accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Noxafil therapy.

3 DOSAGE FORMS AND STRENGTHS

Noxafil injection is available in Type I glass vials closed with bromobutyl rubber stopper and aluminum seal containing 300 mg per 16.7 mL of solution (18 mg of posaconazole per mL).

Noxafil 100 mg delayed-release tablets are available as yellow, coated, oblong tablets, debossed with "100" on one side.

Noxafil oral suspension is available in 4-ounce (123 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Noxafil is contraindicated in persons with known hypersensitivity to posaconazole or other azole antifungal agents.

4.2 Use with Sirolimus

Noxafil is contraindicated with sirolimus. Concomitant administration of Noxafil with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

4.3 QT Prolongation with Concomitant Use with CYP3A4 Substrates

Noxafil is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of Noxafil with the CYP3A4 substrates, pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and cases of torsades de pointes *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

4.5 Use with Ergot Alkaloids

Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism *[see Drug Interactions (7.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Drug Interactions

Concomitant administration of Noxafil with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*. Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

5.2 Arrhythmias and QT Prolongation

Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, cases of torsades de pointes have been reported in patients taking posaconazole.

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18-85 years of age) administered posaconazole oral suspension 400 mg BID with a high-fat meal. In this pooled analysis, the mean QTc (Fridericia) interval change from baseline was –5 msec following administration of the recommended clinical dose. A decrease in the QTc(F) interval (–3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was <0 msec (–8 msec). No healthy subject administered posaconazole had a QTc(F) interval ≥500 msec or an increase ≥60 msec in their QTc(F) interval from baseline.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4 *[see Contraindications (4.3) and Drug Interactions (7.2)]*. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

5.3 Hepatic Toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption. Cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with posaconazole. These severe hepatic reactions were seen primarily in subjects receiving the posaconazole oral suspension 800 mg daily (400 mg BID or 200 mg QID) in clinical trials.

Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

5.4 Renal Impairment

Due to the variability in exposure with Noxafil delayed-release tablets and oral suspension, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)].*

Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the Noxafil injection, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Noxafil therapy *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)]*.

5.5 Use with Midazolam

Concomitant administration of Noxafil with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

5.6 Vincristine Toxicity

Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options *[see Drug Interactions (7.10)]*.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse reactions are discussed in detail in another section of the labeling:

- Hypersensitivity *[see Contraindications (4.1)]*
- Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.3)]*

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of Noxafil cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In clinical trials, the type of adverse reactions reported for

posaconazole injection and posaconazole delayed-release tablets were generally similar to that reported in trials of posaconazole oral suspension.

Clinical Trial Experience with Posaconazole Injection

Multiple doses of posaconazole injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, posaconazole injection was administered via central venous catheter.

The safety of posaconazole injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole injection when given as antifungal prophylaxis (Posaconazole Injection Study 1). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range 18-82 years, 19% of patients were ≥65 years of age), and were 95% white and 8% Hispanic. Ten patients received a single dose of 200 mg posaconazole injection, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days.

Table 6 presents treatment-emergent adverse reactions observed in patients treated with posaconazole injection 300 mg daily dose in the posaconazole injection study. Each patient received a loading dose, 300 mg twice on Day 1. Following posaconazole intravenous therapy, patients received posaconazole oral suspension to complete 28 days of total posaconazole therapy.

Table 6: Posaconazole Injection Study 1: Number (%) of Subjects Treated with Posaconazole Injection 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System **Preferred Term**	**Posaconazole Injection Treatment Phase n=237 (%)***		**Posaconazole Injection Treatment Phase or Subsequent Oral Suspension Treatment Phase n=237(%)†**	
Subjects Reporting any Adverse Reaction	220	(93)	235	(99)
Blood and Lymphatic System Disorder				
Anemia	16	(7)	23	(10)
Thrombocytopenia	17	(7)	25	(11)
Gastrointestinal Disorders				
Abdominal Pain Upper	15	(6)	25	(11)
Abdominal Pain	30	(13)	41	(17)
Constipation	18	(8)	31	(13)
Diarrhea	75	(32)	93	(39)
Nausea	46	(19)	70	(30)
Vomiting	29	(12)	45	(19)
General Disorders and Administration Site Conditions				
Fatigue	19	(8)	24	(10)
Chills	28	(12)	38	(16)
Edema Peripheral	28	(12)	35	(15)
Pyrexia	49	(21)	73	(31)

Metabolism and Nutrition Disorders				
Decreased appetite	23	(10)	29	(12)
Hypokalemia	51	(22)	67	(28)
Hypomagnesemia	25	(11)	30	(13)
Nervous System Disorders				
Headache	33	(14)	49	(21)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	21	(9)	31	(13)
Dyspnea	16	(7)	24	(10)
Epistaxis	34	(14)	40	(17)
Skin and Subcutaneous Tissue Disorders				
Petechiae	20	(8)	24	(10)
Rash	35	(15)	56	(24)
Vascular Disorders				
Hypertension	20	(8)	26	(11)

*Adverse reactions reported in patients with an onset during the posaconazole intravenous dosing phase of the study.
†Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of posaconazole therapy.

The most frequently reported adverse reactions with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily were diarrhea (32%), hypokalemia (22%), pyrexia (21%), and nausea (19%). These adverse reactions were consistent with those seen in studies with Noxafil oral suspension.

Clinical Trial Experience with Posaconazole Delayed-Release Tablets

The safety of posaconazole delayed-release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole delayed-release tablets when given as antifungal prophylaxis (Delayed-Release Tablet Study 1). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17% of patients were ≥65 years of age), and were 93% white and 16% Hispanic. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following twice daily dosing on Day 1 in each cohort). **Table 7** presents treatment-emergent adverse reactions observed in patients treated with 300 mg daily dose at an incidence of ≥10% in posaconazole delayed-release tablet study.

Table 7: Posaconazole Delayed-Release Tablet Study 1: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System **Preferred Term**	**Posaconazole delayed-release tablet (300 mg) (n=210)**	
Subjects Reporting any Adverse Reaction	201	(99)
Blood and Lymphatic System Disorder		
Anemia	22	(10)

Thrombocytopenia	29	(14)
Gastrointestinal Disorders		
Abdominal Pain	23	(11)
Constipation	20	(10)
Diarrhea	61	(29)
Nausea	56	(27)
Vomiting	28	(13)
General Disorders and Administration Site Conditions		
Asthenia	20	(10)
Chills	22	(10)
Mucosal Inflammation	29	(14)
Edema Peripheral	33	(16)
Pyrexia	59	(28)
Metabolism and Nutrition Disorders		
Hypokalemia	46	(22)
Hypomagnesemia	20	(10)
Nervous System Disorders		
Headache	30	(14)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	35	(17)
Epistaxis	30	(14)
Skin and Subcutaneous Tissue Disorders		
Rash	34	(16)
Vascular Disorders		
Hypertension	23	(11)

The most frequently reported adverse reactions (>25%) with posaconazole delayed-release tablets 300 mg once daily were diarrhea, pyrexia, and nausea.

The most common adverse reaction leading to discontinuation of posaconazole delayed-release tablets 300 mg once daily was nausea (2%).

Clinical Trial Safety Experience with Posaconazole Oral Suspension

The safety of posaconazole oral suspension has been assessed in 1844 patients. This includes 605 patients in the active-controlled prophylaxis studies, 557 patients in the active-controlled OPC studies, 239 patients in refractory OPC studies, and 443 patients from other indications. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy, neutropenia post-chemotherapy, GVHD post HSCT, and HIV infection, as well as non-neutropenic patients. This patient population was 71% male, had a mean age of 42 years (range 8-84 years, 6% of patients were ≥65 years of age and 1% was <18 years of age), and were 64% white, 16% Hispanic, and 36% non-white (including 14% black). Posaconazole therapy was given to 171 patients for ≥6 months, with 58 patients receiving posaconazole therapy for ≥12 months. **Table 8** presents treatment-emergent adverse reactions observed at an incidence of >10% in posaconazole prophylaxis studies.

Table 9 presents treatment-emergent adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

Prophylaxis of Aspergillus and Candida: In the 2 randomized, comparative prophylaxis studies (Oral Suspension Studies 1 and 2), the safety of posaconazole oral suspension 200 mg three times a day was compared to fluconazole 400 mg once daily or itraconazole 200 mg twice a day in severely immunocompromised patients.

The most frequently reported adverse reactions (>30%) in the prophylaxis clinical trials were fever, diarrhea, and nausea.

The most common adverse reactions leading to discontinuation of posaconazole in the prophylaxis studies were associated with GI disorders, specifically, nausea (2%), vomiting (2%), and hepatic enzymes increased (2%).

Table 8: Posaconazole Oral Suspension Study 1 and Study 2. Number (%) of Randomized Subjects Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10% in the Posaconazole Oral Suspension or Fluconazole Treatment Groups (Pooled Prophylaxis Safety Analysis)

Body System Preferred Term	Posaconazole (n=605)		Fluconazole (n=539)		Itraconazole (n=58)	
Subjects Reporting any Adverse Reaction	595	(98)	531	(99)	58	(100)
Body as a Whole - General Disorders						
Fever	274	(45)	254	(47)	32	(55)
Headache	171	(28)	141	(26)	23	(40)
Rigors	122	(20)	87	(16)	17	(29)
Fatigue	101	(17)	98	(18)	5	(9)
Edema Legs	93	(15)	67	(12)	11	(19)
Anorexia	92	(15)	94	(17)	16	(28)
Dizziness	64	(11)	56	(10)	5	(9)
Edema	54	(9)	68	(13)	8	(14)
Weakness	51	(8)	52	(10)	2	(3)
Cardiovascular Disorders, General						
Hypertension	106	(18)	88	(16)	3	(5)
Hypotension	83	(14)	79	(15)	10	(17)
Disorders of Blood and Lymphatic System						
Anemia	149	(25)	124	(23)	16	(28)
Neutropenia	141	(23)	122	(23)	23	(40)
Disorders of the Reproductive System and Breast						
Vaginal Hemorrhage*	24	(10)	20	(9)	3	(12)
Gastrointestinal System Disorders						
Diarrhea	256	(42)	212	(39)	35	(60)
Nausea	232	(38)	198	(37)	30	(52)
Vomiting	174	(29)	173	(32)	24	(41)

Abdominal Pain	161	(27)	147	(27)	21	(36)
Constipation	126	(21)	94	(17)	10	(17)
Dyspepsia	61	(10)	50	(9)	6	(10)
Heart Rate and Rhythm Disorders						
Tachycardia	72	(12)	75	(14)	3	(5)
Infection and Infestations						
Pharyngitis	71	(12)	60	(11)	12	(21)
Liver and Biliary System Disorders						
Bilirubinemia	59	(10)	51	(9)	11	(19)
Metabolic and Nutritional Disorders						
Hypokalemia	181	(30)	142	(26)	30	(52)
Hypomagnesemia	110	(18)	84	(16)	11	(19)
Hyperglycemia	68	(11)	76	(14)	2	(3)
Hypocalcemia	56	(9)	55	(10)	5	(9)
Musculoskeletal System Disorders						
Musculoskeletal Pain	95	(16)	82	(15)	9	(16)
Arthralgia	69	(11)	67	(12)	5	(9)
Back Pain	63	(10)	66	(12)	4	(7)
Platelet, Bleeding and Clotting Disorders						
Thrombocytopenia	175	(29)	146	(27)	20	(34)
Petechiae	64	(11)	54	(10)	9	(16)
Psychiatric Disorders						
Insomnia	103	(17)	92	(17)	11	(19)
Respiratory System Disorders						
Coughing	146	(24)	130	(24)	14	(24)
Dyspnea	121	(20)	116	(22)	15	(26)
Epistaxis	82	(14)	73	(14)	12	(21)
Skin and Subcutaneous Tissue Disorders						
Rash	113	(19)	96	(18)	25	(43)
Pruritus	69	(11)	62	(12)	11	(19)
* Percentages of sex-specific adverse reactions are based on the number of males/females.						

HIV Infected Subjects with OPC: In 2 randomized comparative studies in OPC, the safety of posaconazole oral suspension at a dose of less than or equal to 400 mg QD in 557 HIV-infected patients was compared to the safety of fluconazole in 262 HIV-infected patients at a dose of 100 mg QD.

An additional 239 HIV-infected patients with refractory OPC received posaconazole oral suspension in 2 non-comparative trials for refractory OPC (rOPC). Of these subjects, 149 received the 800-mg/day dose and the remainder received the less than or equal to 400-mg QD dose.

In the OPC/rOPC studies, the most common adverse reactions were fever, diarrhea, nausea, headache, vomiting, and coughing.

The most common adverse reactions that led to treatment discontinuation of posaconazole in the Controlled OPC Pool included respiratory impairment (1%) and pneumonia (1%). In the refractory OPC pool, the most common adverse reactions that led to treatment discontinuation of posaconazole were AIDS (7%) and respiratory impairment (3%).

Table 9: Treatment-Emergent Adverse Reactions with Frequency of at Least 10% in OPC Studies with Posaconazole Oral Suspension (Treated Population)

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
Body System	Posaconazole	Fluconazole	Posaconazole
Preferred Term	n=557	n=262	n=239
Subjects Reporting any Adverse Reaction*	356 (64)	175 (67)	221 (92)
Body as a Whole – General Disorders			
Fever	34 (6)	22 (8)	82 (34)
Headache	44 (8)	23 (9)	47 (20)
Anorexia	10 (2)	4 (2)	46 (19)
Fatigue	18 (3)	12 (5)	31 (13)
Asthenia	9 (2)	5 (2)	31 (13)
Rigors	2 (<1)	4 (2)	29 (12)
Pain	4 (1)	2 (1)	27 (11)
Disorders of Blood and Lymphatic System			
Neutropenia	21 (4)	8 (3)	39 (16)
Anemia	11 (2)	5 (2)	34 (14)
Gastrointestinal System Disorders			
Diarrhea	58 (10)	34 (13)	70 (29)
Nausea	48 (9)	30 (11)	70 (29)
Vomiting	37 (7)	18 (7)	67 (28)
Abdominal Pain	27 (5)	17 (6)	43 (18)
Infection and Infestations			
Candidiasis, Oral	3 (1)	1 (<1)	28 (12)
Herpes Simplex	16 (3)	8 (3)	26 (11)
Pneumonia	17 (3)	6 (2)	25 (10)
Metabolic and Nutritional Disorders			
Weight Decrease	4 (1)	2 (1)	33 (14)
Dehydration	4 (1)	7 (3)	27 (11)
Psychiatric Disorders			
Insomnia	8 (1)	3 (1)	39 (16)
Respiratory System Disorders			
Coughing	18 (3)	11 (4)	60 (25)
Dyspnea	8 (1)	8 (3)	28 (12)
Skin and Subcutaneous Tissue Disorders			
Rash	15 (3)	10 (4)	36 (15)
Sweating Increased	13 (2)	5 (2)	23 (10)

OPC=oropharyngeal candidiasis

* Number of subjects reporting treatment-emergent adverse reactions at least once during the study, without regard to relationship to treatment. Subjects may have reported more than 1 event.

Adverse reactions were reported more frequently in the pool of patients with refractory OPC. Among these highly immunocompromised patients with advanced HIV disease, serious adverse reactions (SARs) were reported in 55% (132/239). The most commonly reported SARs were fever (13%) and neutropenia (10%).

Less Common Adverse Reactions: Clinically significant adverse reactions reported during clinical trials in prophylaxis, OPC/rOPC or other trials with posaconazole which occurred in less than 5% of patients are listed below:

- **Blood and lymphatic system disorders:** hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, neutropenia aggravated
- **Endocrine disorders:** adrenal insufficiency
- **Nervous system disorders:** paresthesia
- **Immune system disorders:** allergic reaction *[see Contraindications (4.1)]*
- **Cardiac disorders:** torsades de pointes *[see Warnings and Precautions (5.2)]*
- **Vascular disorders:** pulmonary embolism
- **Gastrointestinal disorders:** pancreatitis
- **Liver and Biliary System Disorders:** bilirubinemia, hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice, AST Increased, ALT Increased
- **Metabolic and Nutritional Disorders:** hypokalemia
- **Platelet, Bleeding, and Clotting Disorders:** thrombocytopenia
- **Renal & Urinary System Disorders:** renal failure acute

Clinical Laboratory Values: In healthy volunteers and patients, elevation of liver function test values did not appear to be associated with higher plasma concentrations of posaconazole.

For the prophylaxis studies, the number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 during the study is presented in **Table 10.**

Table 10: Posaconazole Oral Suspension Study 1 and Study 2. Changes in Liver Function Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4

Number (%) of Patients With Change* Oral Suspension Study 1		
Laboratory Parameter	Posaconazole n=301	Fluconazole n=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
Oral Suspension Study 2		
Laboratory Parameter	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

The number of patients treated for OPC with clinically significant liver function test (LFT) abnormalities at any time during the studies is provided in **Table 11** (LFT abnormalities were present in some of these patients prior to initiation of the study drug).

Table 11: Posaconazole Oral Suspension Studies: Clinically Significant Laboratory Test Abnormalities without Regard to Baseline Value

	Controlled		Refractory
	Posaconazole	Fluconazole	Posaconazole
Laboratory Test	n=557(%)	n=262(%)	n=239(%)
ALT > 3.0 x ULN	16/537 (3)	13/254 (5)	25/226 (11)
AST > 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
Total Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
A kaline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)
ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase.			

6.3 Postmarketing Experience

No clinically significant postmarketing adverse reactions were identified that have not previously been reported during clinical trials experience.

7 DRUG INTERACTIONS

Posaconazole is primarily metabolized via UDP glucuronosyltransferase and is a substrate of p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole *[see Clinical Pharmacology (12.3)]*.

The following information was derived from data with posaconazole oral suspension or early tablet formulation. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole injection as well *[see Drug Interactions (7.9) and (7.13)]*.

7.1 Immunosuppressants Metabolized by CYP3A4

Sirolimus: Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity. Therefore, posaconazole is contraindicated with sirolimus *[see Contraindications (4.2) and Clinical Pharmacology (12.3)]*.

Tacrolimus: Posaconazole has been shown to significantly increase the C_{max} and AUC of tacrolimus. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Cyclosporine: Posaconazole has been shown to increase cyclosporine whole blood concentrations in heart transplant patients upon initiation of posaconazole treatment. It is recommended to reduce cyclosporine dose to approximately three-fourths of the original dose upon initiation of posaconazole treatment. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 CYP3A4 Substrates

Concomitant administration of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and cases of torsades de pointes. Therefore, posaconazole is contraindicated with these drugs *[see Contraindications (4.3) and Warnings and Precautions (5.2)]*.

7.3 HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4

Concomitant administration of posaconazole with simvastatin increases the simvastatin plasma concentrations by approximately 10-fold. Therefore, posaconazole is contraindicated with HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 *[see Contraindications (4.4) and Clinical Pharmacology (12.3)]*.

7.4 Ergot Alkaloids

Most of the ergot alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Therefore, posaconazole is contraindicated with ergot alkaloids *[see Contraindications (4.5)]*.

7.5 Benzodiazepines Metabolized by CYP3A4

Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant use of posaconazole and other benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of these benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4 and benzodiazepine receptor antagonists must be available to reverse these effects *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

7.6 Anti-HIV Drugs

Efavirenz: Efavirenz induces UDP-glucuronidase and significantly decreases posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)]*. It is recommended to avoid concomitant use of efavirenz with posaconazole unless the benefit outweighs the risks.

Ritonavir and Atazanavir: Ritonavir and atazanavir are metabolized by CYP3A4 and posaconazole increases plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)]*. Frequent monitoring of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration with posaconazole.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended *[see Clinical Pharmacology (12.3)]*.

7.7 Rifabutin

Rifabutin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Rifabutin is also metabolized by CYP3A4. Therefore, coadministration of rifabutin with posaconazole increases rifabutin plasma concentrations *[see Clinical Pharmacology (12.3)]*. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections as well as frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) are recommended.

7.8 Phenytoin

Phenytoin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Phenytoin is also metabolized by CYP3A4. Therefore, coadministration of phenytoin with posaconazole increases phenytoin plasma concentrations *[see Clinical Pharmacology (12.3)]*. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended and frequent monitoring of phenytoin concentrations should be performed while coadministered with posaconazole and dose reduction of phenytoin should be *considered*.

7.9 Gastric Acid Suppressors/Neutralizers

Posaconazole Delayed-Release Tablet:

No clinically relevant effects on the pharmacokinetics of posaconazole were observed when posaconazole delayed-release tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of posaconazole delayed-release tablets is required when posaconazole delayed-release tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors.

Posaconazole Oral Suspension:

Cimetidine (an H_2-receptor antagonist) and esomeprazole (a proton pump inhibitor) when given with posaconazole oral suspension results in decreased posaconazole plasma concentrations *[see Clinical*

Pharmacology (12.3)]. It is recommended to avoid concomitant use of cimetidine and esomeprazole with posaconazole oral suspension unless the benefit outweighs the risks. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.

No clinically relevant effects were observed when posaconazole oral suspension is concomitantly used with antacids and H_2-receptor antagonists other than cimetidine. No dosage adjustment of posaconazole oral suspension is required when posaconazole oral suspension is concomitantly used with antacids and H_2-receptor antagonists other than cimetidine.

7.10 Vinca Alkaloids

Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with serious adverse reactions *[see Warnings and Precautions (5.6)].* Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

7.11 Calcium Channel Blockers Metabolized by CYP3A4

Posaconazole may increase the plasma concentrations of calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, diltiazem, nifedipine, nicardipine, felodipine). Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during coadministration. Dose reduction of calcium channel blockers may be needed.

7.12 Digoxin

Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, monitoring of digoxin plasma concentrations is recommended during coadministration.

7.13 Gastrointestinal Motility Agents

Posaconazole Delayed-Release Tablet:

Concomitant administration of metoclopramide with posaconazole delayed-release tablets did not affect the pharmacokinetics of posaconazole *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of posaconazole delayed-release tablets is required when given concomitantly with metoclopramide.

Posaconazole Oral Suspension:

Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)].* If metoclopramide is concomitantly administered with posaconazole oral suspension, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations after posaconazole oral suspension administration *[see Clinical Pharmacology (12.3)].* No dosage adjustment of posaconazole is required when loperamide and posaconazole are used concomitantly.

7.14 Glipizide

Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when posaconazole and glipizide are concomitantly used.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women. Noxafil should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses ≥27 mg/kg (≥1.4 times the 400-mg BID oral suspension regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400-mg BID oral suspension regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the exposure achieved with the 400-mg BID oral suspension regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

8.3 Nursing Mothers

Posaconazole is excreted in milk of lactating rats. It is not known whether Noxafil is excreted in human milk. Because of the potential for serious adverse reactions from Noxafil in nursing infants, a decision

should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Noxafil injection in pediatric patients below the age of 18 years of age has not been established. Noxafil injection should not be used in pediatric patients because of nonclinical safety concerns *[see Nonclinical Toxicology (13.2)]*.

The safety and effectiveness of posaconazole oral suspension and posaconazole delayed-release tablets have been established in the age groups 13 to 17 years of age. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults. The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years (birth to 12 years) have not been established.

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension for prophylaxis of invasive fungal infections. The safety profile in these patients <18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state average posaconazole concentration (Cavg) was similar between these patients and adults (≥18 years of age). In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with posaconazole oral suspension, the exposure target of steady-state posaconazole Cavg between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.

8.5 Geriatric Use

Of the 279 patients treated with posaconazole injection, 52 (19%) were greater than 65 years of age. The pharmacokinetics of posaconazole injection are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for Noxafil injection in geriatric patients.

Of the 230 patients treated with posaconazole delayed-release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole delayed-release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Of the 605 patients randomized to posaconazole oral suspension in the prophylaxis clinical trials, 63 (10%) were ≥65 years of age. In addition, 48 patients treated with greater than or equal to 800-mg/day posaconazole in another indication were ≥65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients.

The pharmacokinetics of posaconazole oral suspension are comparable in young and elderly subjects (≥65 years of age); therefore no adjustment in the dosage of Noxafil oral suspension is necessary in geriatric patients.

No overall differences in the pharmacokinetics and safety were observed between elderly and young subjects during clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (eGFR: 50-80 mL/min/1.73 m^2, n=6) or moderate (eGFR: 20-49 mL/min/1.73 m^2, n=6) renal impairment on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal impairment (eGFR: <20 mL/min/1.73 m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (eGFR: >80 mL/min/1.73 m^2); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal impairment as compared to that in the other renal impairment groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2)]*. Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with the delayed-release tablets.

Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the Noxafil injection, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be

closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Noxafil therapy *[see Dosage and Administration (2.6) and Warnings and Precautions (5.4)]*.

8.7 Hepatic Impairment

After a single oral dose of posaconazole oral suspension 400 mg, the mean AUC was 43%, 27%, and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), or severe (Child-Pugh Class C, N=6) hepatic impairment, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean C_{max} was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, or severe hepatic impairment, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The elimination half-life ($t_{½}$) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment, respectively.

It is recommended that no dose adjustment of Noxafil is needed in patients with mild to severe hepatic impairment (Child-Pugh Class A, B, or C) *[see Dosage and Administration (2)* and *Warnings and Precautions (5.3)]*. Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with the delayed-release tablets.

Similar recommendations apply to posaconazole injection; however, a specific study has not been conducted with the posaconazole injection.

8.8 Gender

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of Noxafil is necessary based on gender.

8.9 Race

The pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of Noxafil is necessary based on race.

8.10 Weight

Pharmacokinetic modeling suggests that patients weighing greater than 120 kg may have lower posaconazole plasma drug exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections.

10 OVERDOSAGE

There is no experience with overdosage of posaconazole injection and delayed-release tablets.

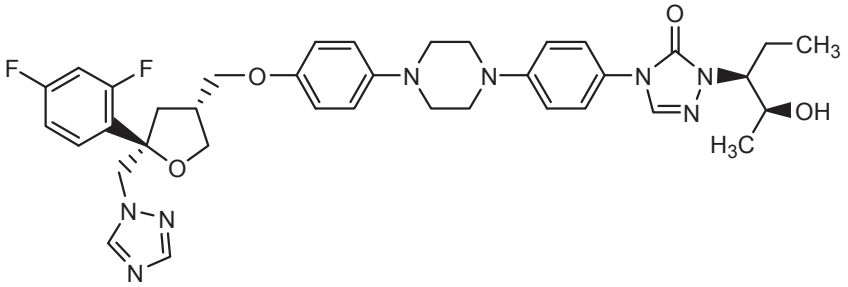
During the clinical trials, some patients received posaconazole oral suspension up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg BID posaconazole oral suspension for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Noxafil is an azole antifungal agent available as concentrated solution to be diluted before intravenous administration, delayed-release tablet, or suspension for oral administration.

Posaconazole is designated chemically as 4-[4-[4-[4-[[(3*R*,5*R*)-5- (2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



Posaconazole is a white powder with a low aqueous solubility.

Noxafil injection is available as a clear colorless to yellow, sterile liquid essentially free of foreign matter. Each vial contains 300 mg of posaconazole and the following inactive ingredients: 6.68 g Betadex Sulfobutyl Ether Sodium (SBECD), 0.003 g edetate disodium, hydrochloric acid and sodium hydroxide to adjust the pH to 2.6, and water for injection.

Noxafil delayed-release tablet is a yellow, coated, oblong tablet containing 100 mg of posaconazole. Each delayed-release tablet contains the inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow).

Noxafil oral suspension is a white, cherry-flavored immediate-release suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerin, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavor, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Posaconazole is an azole antifungal agent *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

Exposure Response Relationship: In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), a wide range of plasma exposures to posaconazole was noted following administration of Noxafil oral suspension. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cavg) and prophylactic efficacy (**Table 12**). A lower Cavg may be associated with an increased risk of treatment failure, defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections.

Table 12: Noxafil Oral Suspension Exposure Analysis (Cavg) in Prophylaxis Trials

	Prophylaxis in AML/MDS*		Prophylaxis in GVHD†	
	Cavg Range (ng/mL)	Treatment Failure‡ (%)	Cavg Range (ng/mL)	Treatment Failure‡ (%)
Quartile 1	90-322	54.7	22-557	44.4
Quartile 2	322-490	37.0	557-915	20.6
Quartile 3	490-734	46.8	915-1563	17.5
Quartile 4	734-2200	27.8	1563-3650	17.5

Cavg = the average posaconazole concentration when measured at steady state
* Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS
† HSCT recipients with GVHD
‡ Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

Posaconazole Injection

Posaconazole injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers and patients. The mean pharmacokinetic parameters after single doses with posaconazole injection in healthy volunteers and patients are shown in **Table 13**.

Table 13: Summary of Mean Pharmacokinetic Parameters (%CV) in Healthy Volunteers (30 minute infusion via peripheral venous line) and Patients (90 minute infusion via central venous line) after Dosing with Posaconazole Injection on Day 1

	Dose (mg)	n	$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	CL (L/hr)
Healthy Volunteers	200	9	35400 (50)	8840 (20)	2250 (29)	23.6 (23)	6.5 (32)
	300	9	46400 (26)	13000 (13)	2840 (30)	24.6 (20)	6.9 (27)
Patients	200	30	N/D	5570 (32)	954 (44)	N/D	N/D
	300	22	N/D	8240 (26)	1590 (62)	N/D	N/D

$AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-12} = Area under the plasma concentration-time curve from time zero to 12 hr after the first dose on Day 1; C_{max} = maximum observed concentration; $t_{½}$ = terminal phase half-life; CL = total body clearance; N/D = Not Determined

Table 14 displays the pharmacokinetic parameters of posaconazole in patients following administration of posaconazole injection 300 mg taken once a day for 10 or 14 days following BID dosing on Day 1.

Table 14: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaconazole Injection (300 mg)*

Day	N	C_{max} (ng/mL)	T_{max}† (hr)	AUC_{0-24} (ng*hr/mL)	Cav (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

AUC_{0-24} = area under the concentration-time curve over the dosing interval (i.e. 24 hours); Cav= time-averaged concentrations (i.e., AUC_{0-24h}/24hr);

C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max} = observed maximum plasma concentration; CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; T_{max} = time of observed maximum plasma concentration.

* 300 mg dose administered over 90 minutes once a day following BID dosing on Day 1

† Median (minimum-maximum)

Posaconazole Delayed-Release Tablets

Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. The mean pharmacokinetic parameters of posaconazole at steady state following administration of Noxafil delayed-release tablets 300 mg twice daily (BID) on Day 1, then 300 mg once daily (QD) thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD are shown in **Table 15**.

Table 15: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Posaconazole Delayed-Release Tablets (300 mg)*

	N	$AUC_{0-24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-T} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; $t_{½}$ = terminal phase half-life; CL /F = Apparent total body clearance

*300 mg BID on Day 1, then 300 mg QD thereafter

† Cav = time-averaged concentrations (i.e., $AUC_{0-24\ hr}$/24hr)

‡ Median (minimum-maximum)

Posaconazole Oral Suspension

Dose-proportional increases in plasma exposure (AUC) to posaconazole oral suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg BID to 400 mg BID in healthy volunteers. No further increases in exposure were observed when the dose of the oral suspension increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal infections.

The mean (%CV) [min-max] posaconazole oral suspension average steady-state plasma concentrations (Cavg) and steady-state pharmacokinetic parameters in patients following administration of 200 mg TID and 400 mg BID of the oral suspension are provided in **Table 16.**

Table 16: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole Oral Suspension 200 mg TID and 400 mg BID

Dose*	Cavg (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{½}$ (hr)
200 mg TID‡ (n=252)	1103 (67) [21.5-3650]	ND§	ND§	ND§	ND§
200 mg TID¶ (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg BID# (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Cavg = the average posaconazole concentration when measured at steady state
* Oral suspension administration
† $AUC_{(0\text{-}24\ hr)}$ for 200 mg TID and $AUC_{(0\text{-}12\ hr)}$ for 400 mg BID
‡ HSCT recipients with GVHD
§ Not done
¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
# Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Absorption:

Posaconazole Delayed-Release Tablets

When given orally in healthy volunteers, posaconazole delayed-release tablets are absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BID loading dose at Day 1). The absolute bioavailability of the oral delayed-release tablet is approximately 54% under fasted conditions. The C_{max} and AUC of posaconazole following administration of posaconazole delayed-release tablets is increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see **Table 17**). In order to enhance the oral absorption of posaconazole and optimize plasma concentrations, posaconazole delayed-release tablets should be administered with food.

Table 17: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg Posaconazole Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

	Fasting Conditions		Fed Conditions (High Fat Meal)*		Fed/Fasting
Pharmacokinetic Parameter	**N**	**Mean (%CV)**	**N**	**Mean (%CV)**	**GMR (90% CI)**
C_{max} (ng/mL)	14	935 (34)	16	1060 (25)	1.16 (0.96, 1.41)
$AUC_{0\text{-}72hr}$ (hr·ng/mL)	14	26200 (28)	16	38400 (18)	1.51 (1.33, 1.72)
T_{max}† (hr)	14	5.00 (3.00, 8.00)	16	6.00 (5.00, 24.00)	N/A

GMR=Geometric least-squares mean ratio; CI=Confidence interval
* 48.5 g fat
† Median (Min, Max) reported for T_{max}

Concomitant administration of posaconazole delayed-release tablets with drugs affecting gastric pH or gastric motility did not demonstrate any significant effects on posaconazole pharmacokinetic exposure (see **Table 18**).

Table 18: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Posaconazole Delayed-Release Tablets in Healthy Volunteers

Coadministered Drug	Administration Arms	Change in C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in $AUC_{0\text{-last}}$ (ratio estimate*; 90% CI of the ratio estimate)
Mylanta® Ultimate strength liquid (Increase in gastric pH)	25.4 meq/5 mL, 20 mL	↑6% (1.06; 0.90 -1.26)↑	↑4% (1.04; 0.90 -1.20)
Ranitidine (Zantac®) (Alteration in gastric pH)	150 mg (morning dose of 150 mg Ranitidine BID)	↑4% (1.04; 0.88 -1.23)↑	↓3% (0.97; 0.84 -1.12)
Esomeprazole (Nexium®) (Increase in gastric pH)	40 mg (QAM 5 days, day -4 to 1)	↑2% (1.02; 0.88-1.17)↑	↑5% (1.05; 0.89 -1.24)
Metoclopramide (Reglan®) (Increase in gastric motility)	15 mg four times daily during 2 days (Day -1 and 1)	↓14% (0.86, 0.73,1.02)	↓7% (0.93, 0.803,1.07)

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to posaconazole alone for C_{max} or $AUC_{0\text{-last}}$.

Posaconazole Oral Suspension

Posaconazole oral suspension is absorbed with a median T_{max} of ~3 to 5 hours. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when the oral suspension is administered with a nonfat meal and approximately 4-times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of posaconazole oral suspension 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see **Table 19**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of posaconazole oral suspension in healthy volunteers have been investigated and are shown in **Table 20**.

In order to assure attainment of adequate plasma concentrations, it is recommended to administer Noxafil oral suspension during or immediately following a full meal. In patients who cannot eat a full meal, Noxafil oral suspension should be taken with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).

Table 19: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Oral Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	T_{max}* (hr)	AUC (I) (ng·hr/mL)	CL/F (L/hr)	$t_{½}$ (hr)
200 mg fasted (n=20)†	132 (50) [45-267]	3.50 [1.5-36‡]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20)†	378 (43) [131-834]	4 [3-5]	10,753 (35) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]

200 mg high fat (54 gm fat) (n=20)[†]	512 (34) [241-1016]	5 [4-5]	15,059 (26) [10,341-24,476]	14 (24) [8.2-19]	23.0 (19) [17.2-33.4]
400 mg fasted (n=23)[§]	121 (75) [27-366]	4 [2-12]	5258 (48) [2834-9567]	91 (40) [42-141]	27.3 (26) [16.8-38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)[§]	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

* Median [min-max].
[†] n=15 for AUC (I), CL/F, and $t_{½}$
[‡] The subject with T_{max} of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs).
[§] n=10 for AUC (I), CL/F, and $t_{½}$

Table 20: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Posaconazole Oral Suspension in Healthy Volunteers*

Study Description	Administration Arms	Change in C_{max} (ratio estimate[†]; 90% CI of the ratio estimate)	Change in AUC (ratio estimate[†]; 90% CI of the ratio estimate)
400-mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48-2.59)	↑111% (2.11; 1.60-2.78)
	During high-fat meal	↑339% (4.39; 3.32-5.80)	↑382% (4.82; 3.66-6.35)
	20 minutes after high-fat meal	↑333% (4.33; 3.28-5.73)	↑387% (4.87; 3.70-6.42)
400 mg BID and 200 mg QID for 7 days in fasted state and with liquid nutritional supplement (BOOST®) (n=12)	400 mg BID with BOOST	↑65% (1.65; 1.29-2.11)	↑66% (1.66; 1.30-2.13)
	200 mg QID with BOOST	No Effect	No Effect
Divided daily dose from 400 mg BID to 200 mg QID for 7 days regardless of fasted conditions or with BOOST (n=12)	Fasted state	↑136% (2.36; 1.84-3.02)	↑161% (2.61; 2.04-3.35)
	With BOOST	↑137% (2.37; 1.86-3.04)	↑157% (2.57; 2.00-3.30)
400-mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	Ginger ale	↑92% (1.92; 1.51-2.44)	↑70% (1.70; 1.43-2.03)
	Esomeprazole	↓32% (0.68; 0.53-0.86)	↓30% (0.70; 0.59-0.83)
400-mg single dose with a prokinetic agent (metoclopramide 10 mg TID for 2 days) + BOOST or an antikinetic agent (loperamide 4-mg single dose) + BOOST (n=12)	With metoclopramide + BOOST	↓21% (0.79; 0.72-0.87)	↓19% (0.81; 0.72-0.91)
	With loperamide + BOOST	↓3% (0.97; 0.88-1.07)	↑11% (1.11; 0.99-1.25)
400-mg single dose either orally with BOOST or via an NG tube with BOOST (n=16)	Via NG tube[‡]	↓19% (0.81; 0.71-0.91)	↓23% (0.77; 0.69-0.86)

* In 5 subjects, the C_{max} and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when

Noxafil was administered via an NG tube compared to when Noxafil was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when Noxafil is administered via an NG tube because a lower plasma exposure may be associated with an increased risk of treatment failure.
† Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for C_{max} or AUC.
‡ NG = nasogastric

Concomitant administration of posaconazole oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (See **Table 21.**)

Table 21: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Posaconazole Oral Suspension in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Cimetidine (Alteration of gastric pH)	400 mg BID × 10 days	200 mg (tablets) QD × 10 days†	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)
Esomeprazole (Increase in gastric pH)‡	40 mg QAM × 3 days	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)
Metoclopramide (Increase in gastric motility)‡	10 mg TID × 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for C_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.

Distribution:

The mean volume of distribution of posaconazole after intravenous solution administration was 261 L and ranged from 226-295 L between studies and dose levels.

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin.

Metabolism:

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically with the oral suspension or an early tablet formulation, which affect posaconazole concentrations, is provided in **Table 22.**

Table 22: Summary of the Effect of Coadministered Drugs on Posaconazole in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G Induction)	400 mg QD × 10 and 20 days	400 mg (oral suspension) BID × 10 and 20 days	↓45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)

Fosamprenavir (unknown mechanism)	700 mg BID x 10 days	200 mg QD on the 1st day, 200 mg BID on the 2nd day, then 400 mg BID x 8 Days	↓21% 0.79 (0.71-0.89)	↓23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg QD x 17 days	200 mg (tablets) QD × 10 days†	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg QD x 10 days	200 mg (tablets) QD × 10 days†	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)
* Ratio Estimate is the ratio of coadministered drug plus posaconazole to posaconazole alone for C_{max} or AUC. † The tablet refers to a non-commercial tablet formulation without polymer.				

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **Table 23** *[see Contraindications (4)* and *Drug Interactions (7.1) including recommendations]*.

Table 23: Summary of the Effect of Posaconazole on Coadministered Drugs in Healthy Volunteers and Patients

Coadministered Drug (Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)	**Coadministered Drug Dose/Schedule**	**Posaconazole Dose/ Schedule**	**Effect on Bioavailability of Coadministered Drugs**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Sirolimus	2-mg single oral dose	400 mg (oral suspension) BID x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
Cyclosporine	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD x 10 days†	↑ cyclosporine whole blood trough concentrations Cyclosporine dose reductions of up to 29% were required	
Tacrolimus	0.05-mg/kg single oral dose	400 mg (oral suspension) BID × 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)
Simvastatin	40-mg single oral dose	100 mg (oral suspension) QD x 13 days	Simvastatin ↑ 841% (9.41, 7.13-12.44) Simvastatin Acid ↑ 817% (9.17, 7.36-11.43)	Simvastatin ↑ 931% (10.31, 8.40-12.67) Simvastatin Acid ↑634% (7.34, 5.82-9.25)
		200 mg (oral suspension) QD x 13 days	Simvastatin ↑ 1041% (11.41, 7.99-16.29) Simvastatin Acid ↑851% (9.51, 8.15-11.10)	Simvastatin ↑ 960% (10.60, 8.63-13.02) Simvastatin Acid ↑748% (8.48, 7.04-10.23)

Midazolam	0.4-mg single intravenous dose‡	200 mg (oral suspension) BID x 7 days	↑ 30% (1.3; 1.13-1.48)	↑ 362% (4.62; 4.02-5.3)
	0.4-mg single intravenous dose‡	400 mg (oral suspension) BID x 7 days	↑62% (1.62; 1.41-1.86)	↑524% (6.24; 5.43-7.16)
	2-mg single oral dose‡	200 mg (oral suspension) QD x 7 days	↑ 169% (2.69; 2.46-2.93)	↑ 470% (5.70; 4.82-6.74)
	2-mg single oral dose‡	400 mg (oral suspension) BID x 7 days	↑ 138% (2.38; 2.13-2.66)	↑ 397% (4.97; 4.46-5.54)
Rifabutin	300 mg QD x 17 days	200 mg (tablets) QD × 10 days†	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72;1.51-1.95)
Phenytoin	200 mg QD PO x 10 days	200 mg (tablets) QD x 10 days†	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)
Ritonavir	100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 49% (1.49; 1.04-2.15)	↑ 80% (1.8;1.39-2.31)
Atazanavir	300 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)
Atazanavir/ ritonavir boosted regimen	300 mg/100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 53% (1.53; 1.13-2.07)	↑ 146% (2.46; 1.93-3.13)

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for C_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with posaconazole.

Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir, or caffeine were observed when administered with posaconazole 200 mg QD; therefore, no dose adjustments are required for these coadministered drugs when coadministered with posaconazole 200 mg QD.

Excretion:

Following administration of Noxafil oral suspension, posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug).

Posaconazole injection is eliminated with a mean terminal half-life ($t_{½}$) of 27 hours and a total body clearance (CL) of 7.3 L/h.

Posaconazole delayed-release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 to 31 hours.

Posaconazole oral suspension is eliminated with a mean half-life ($t_{½}$) of 35 hours (range: 20-66 hours).

12.4 Microbiology

Mechanism of Action:

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

Resistance:

Clinical isolates of *Candida albicans* and *Candida glabrata* with decreased susceptibility to posaconazole were observed in oral swish samples taken during prophylaxis with posaconazole and fluconazole, suggesting a potential for development of resistance. These isolates also showed reduced susceptibility to other azoles, suggesting cross-resistance between azoles. The clinical significance of this finding is not known.

Antimicrobial Activity:
Posaconazole has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.
Microorganisms:
Aspergillus spp. and *Candida spp.*
Susceptibility testing:
Posaconazole interpretive criteria (breakpoints) have not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9- or 3.5-times the exposure achieved with a 400-mg BID oral suspension regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400-mg BID oral suspension regimen). In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8-times the exposure achieved with a 400-mg BID oral suspension regimen.

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400-mg BID oral suspension regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400-mg BID oral suspension regimen).

13.2 Animal Toxicology and/or Pharmacology

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age), an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age).

The clinical significance of this finding is unknown; therefore, the use of posaconazole injection to patients under 18 years of age is not recommended.

14 CLINICAL STUDIES

14.1 Prophylaxis of *Aspergillus* and *Candida* Infections with Posaconazole Oral Suspension

Two randomized, controlled studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Oral Suspension Study 1) was a randomized, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, posaconazole; 77 days, fluconazole). **Table 24** contains the results from Oral Suspension Study 1.

Table 24: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD): Oral Suspension Study 1

	Posaconazole n=301	Fluconazole n=299

On therapy plus 7 days		
Clinical Failure*	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths Proven/probable fungal infection prior to death	22 (7%) 2 (<1%)	24 (8%) 6 (2%)
SAF†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths Proven/probable fungal infection prior to death	58 (19%) 10 (3%)	59 (20%) 16 (5%)
SAF†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).
§ Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (Oral Suspension Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS. As in Oral Suspension Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). This study assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **Table 25** contains the results from Oral Suspension Study 2.

Table 25: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia: Oral Suspension Study 2

	Posaconazole n=304	**Fluconazole/Itraconazole n=298**
On therapy plus 7 days		
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths Proven/probable fungal infection prior to death	17 (6%) 1 (<1%)	25 (8%) 2 (1%)
SAF‡	67 (22%)	98 (33%)
Through 100 days postrandomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)

(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).
§ Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted with the posaconazole oral suspension. As seen in the accompanying tables (**Tables 24 and 25**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Oral Suspension Study 1 (**Table 24**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Oral Suspension Study 2 (**Table 25**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to -7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for posaconazole-treated patients in Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated substantially fewer breakthrough infections caused by *Aspergillus* species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

14.2 Treatment of Oropharyngeal Candidiasis with Posaconazole Oral Suspension

Posaconazole Oral Suspension Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (see **Table 26**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (see **Table 26**).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, Day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see **Table 26**).

Table 26: Posaconazole Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

	Posaconazole	Fluconazole
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

14.3 Posaconazole Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Posaconazole Oral Suspension Study 4 was a noncomparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole greater than or equal to 100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole oral suspension 400 mg BID for 3 days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg BID for 28 days. The efficacy of posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

Injection

Noxafil injection is available in Type I glass vials closed with bromobutyl rubber stopper and aluminum seal (NDC 0085-4331-01) containing 300 mg per 16.7 mL of solution (18 mg of posaconazole per mL). Store refrigerated at 2-8°C (36-46°F).

Delayed-Release Tablets

Noxafil 100 mg delayed-release tablets; yellow, coated, oblong, debossed with "100" on one side. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0085-4324-02). Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Oral Suspension

Noxafil oral suspension is available in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0085-1328-01) containing 105 mL of suspension (40 mg of posaconazole per mL).

Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]**. DO NOT FREEZE.**

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

17.1 Administration

Noxafil Delayed-Release Tablets

Advise patients to take Noxafil delayed-release tablets with food.

Advise patients that Noxafil delayed-release tablets must be swallowed whole and not divided, crushed, or chewed.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 12 hours of the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil Oral Suspension

Advise patients to take each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of Noxafil oral suspension should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in order to enhance absorption.

Instruct patients that if they miss a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

17.2 Drug Interactions

Advise patients to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.
- are currently taking a cyclosporine or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.
- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

17.3 Serious and Potentially Serious Adverse Reactions

Advise patients to inform their physician immediately if they:

- notice a change in heart rate or heart rhythm, or have a heart condition or circulatory disease. Posaconazole can be administered with caution to patients with potentially proarrhythmic conditions.
- are pregnant, plan to become pregnant, or are nursing.
- have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Injection: Manuf. by: MSD International GmbH, Brinny, Innishannon, County Cork, Ireland

Delayed-Release Tablets: Manuf. by: N. V. Organon, Kloosterstraat 6, 5349 AB Oss, Netherlands

Oral Suspension: Manuf. by: Patheon Inc., Whitby, Ontario, Canada L1N 5Z5

For patent information: www.merck.com/product/patent/home.html

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1.6.2.2.2　　欧州連合添付文書（原文）

1.6.2.2.2.1　　経口懸濁液

2018年7月版の添付文書を添付する。
（POS_EUSPC_NOXAFIL-OS.pdf）

Confidential

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 40 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 40 mg of posaconazole.

Excipient with known effect:
This medicinal product contains approximately 1.75 g of glucose per 5 mL of suspension.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil oral suspension is indicated for use in the treatment of the following fungal infections in adults (see section 5.1):
- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;
- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil oral suspension is also indicated for prophylaxis of invasive fungal infections in the following patients:
- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

4.2 Posology and method of administration

Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension

The tablet and oral suspension are not to be used interchangeably due to the differences between these

two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Posology

Noxafil is also available as 100 mg gastro-resistant tablet and 300 mg concentrate for solution for infusion. Noxafil tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than Noxafil oral suspension.

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	200 mg (5 mL) four times a day. Alternatively, patients who can tolerate food or a nutritional supplement may take 400 mg (10 mL) twice a day during or immediately following a meal or nutritional supplement. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Oropharyngeal candidiasis	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. Each dose of Noxafil should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure.
Prophylaxis of invasive fungal infections	200 mg (5 mL) three times a day. Each dose of Noxafil should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.

Special populations

Renal impairment

An effect of renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (see section 5.2).

Hepatic impairment

Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil in children aged below 18 years have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration
For oral use

The oral suspension must be shaken well before use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see sections 4.4 and 4.5).

Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity
There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Noxafil to patients with hypersensitivity to other azoles.

Hepatic toxicity
Hepatic reactions (e.g. mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.
Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of Noxafil should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation
Some azoles have been associated with prolongation of the QTc interval. Noxafil must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Noxafil should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure

- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in section 4.3).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Drug Interactions
Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see section 4.5).

Midazolam and other benzodiazepines
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Vincristine Toxicity
Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see section 4.5).

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), efavirenz and cimetidine
Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Gastrointestinal dysfunction
There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

Excipients
This medicinal product contains approximately 1.75 g of glucose per 5 mL of suspension. Patients with glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on posaconazole
Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux *in vitro*. Therefore, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these clearance pathways may increase or decrease posaconazole plasma concentrations, respectively.

Rifabutin
Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole to 57 % and 51 %, respectively. Concomitant use of posaconazole and rifabutin and similar inducers (e.g. rifampicin) should be avoided unless the benefit to the patient outweighs the risk. See also below regarding the effect of posaconazole on rifabutin plasma levels.

Efavirenz
Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir
Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin and similar inducers (e.g. carbamazepine, phenobarbital, primidone) should be avoided unless the benefit to the patient outweighs the risk.

H_2 receptor antagonists and proton pump inhibitors
Posaconazole plasma concentrations (C_{max} and AUC) were reduced by 39 % when posaconazole was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to a decrease in gastric acid production. Co-administration of posaconazole with H_2 receptor antagonists should be avoided if possible.
Similarly, administration of 400 mg posaconazole with esomeprazole (40 mg daily) decreased mean C_{max} and AUC by 46 % and 32 %, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of posaconazole with proton pump inhibitors should be avoided if possible.

Food
The absorption of posaconazole is significantly increased by food (see sections 4.2 and 5.2).

Effects of posaconazole on other medicinal products
Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates may result in large increases in exposure to CYP3A4 substrates as exemplified by the effects on tacrolimus, sirolimus, atazanavir and midazolam below. Caution is advised during co-administration of posaconazole with CYP3A4 substrates administered intravenously and the dose of the CYP3A4 substrate may need to be reduced. If posaconazole is used concomitantly with CYP3A4 substrates that are administered orally, and for which an increase in plasma concentrations may be associated with unacceptable adverse reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions should be closely monitored and the dose adjusted as needed. Several of the interaction studies were conducted in healthy volunteers in whom a higher exposure to posaconazole occurs compared to patients administered the same dose. The effect of posaconazole on CYP3A4 substrates in patients might be somewhat lower than that observed in healthy volunteers, and is expected to be variable between patients due to the variable posaconazole exposure in patients. The effect of co-administration with posaconazole on plasma levels of CYP3A4 substrates may also be variable within a patient, unless posaconazole is administered in a strictly standardised way with food, given the large food effect on posaconazole exposure (see section 5.2).

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates)
Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see section 4.3).

Ergot alkaloids
Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin)
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis (see section 4.3).

Vinca alkaloids
Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of posaconazole oral suspension (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold (range 3.1 to 17.5-fold), respectively, in healthy subjects. The effect of posaconazole on sirolimus in patients is unknown, but is expected to be variable due to the variable posaconazole exposure in patients. Co-administration of posaconazole with sirolimus is not recommended and should be avoided whenever possible. If it is considered that co-administration is unavoidable, then it is recommended that the dose of sirolimus should be greatly reduced at the time of initiation of posaconazole therapy and that there should be very frequent monitoring of trough concentrations of sirolimus in whole blood. Sirolimus concentrations should be measured upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly**.** It should be noted that the relationship between sirolimus trough concentration and AUC is changed during co-administration with posaconazole. As a result, sirolimus trough concentrations that fall within the usual therapeutic range may result in sub-therapeutic levels. Therefore trough concentrations that fall in the upper part of the usual therapeutic range should be targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin should be adjusted as necessary.

Tacrolimus
Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

HIV Protease inhibitors
As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir (300 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 2.6-fold and 3.7-fold (range 1.2 to 26-fold), respectively. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir and ritonavir (300/100 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 1.5-fold and 2.5-fold (range 0.9 to 4.1-fold), respectively. The addition of posaconazole to therapy with atazanavir or with atazanavir plus ritonavir was associated with increases in plasma bilirubin levels. Frequent monitoring for adverse reactions and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Midazolam and other benzodiazepines metabolised by CYP3A4
In a study in healthy volunteers posaconazole oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole oral suspension 400 mg twice daily for 7 days increased the intravenous midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, posaconazole oral suspension (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration.
Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin
Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas
Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential have to use effective contraception during treatment. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding
Posaconazole is excreted into the milk of lactating rats (see section 5.3). The excretion of posaconazole in human breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with posaconazole.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (1.7 times the 400-mg twice daily regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 times the 400-mg twice daily regimen). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Summary of the safety profile

The safety of posaconazole oral suspension has been assessed in > 2,400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. The most frequently reported serious related adverse reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.
The safety of posaconazole tablet has been assessed in 336 patients and healthy volunteers enrolled in clinical trials. The safety profile of tablets was similar to that of the oral suspension.

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
Rare:	haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy, haemorrhage
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction

Endocrine disorders	
Rare:	adrenal insufficiency, blood gonadotropin decreased
Metabolism and nutrition disorders	
Common:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common:	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
Rare:	gastrointestinal haemorrhage, ileus
Hepatobiliary disorders	
Common:	liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased)
Uncommon:	hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis

Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	breast pain
General disorders and administration site conditions	
Common:	pyrexia (fever), asthenia, fatigue
Uncommon:	oedema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, mucosal inflammation
Rare:	tongue oedema, face oedema
Investigations	
Uncommon:	altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

§ See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance of posaconazole oral suspension, severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC04.

Mechanism of action
Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology
Posaconazole has been shown *in vitro* to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor*, *Mucor*, and *Rhizopus.* The microbiological data suggest that posaconazole is active against *Rhizomucor*, *Mucor*, and *Rhizopus;* however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Resistance
Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Epidemiological Cut-off (ECOFF) Values for *Aspergillus* spp.
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

Combination with other antifungal agents
The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Pharmacokinetic / Pharmacodynamic relationships
A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see sections 4.2 and 5.2 on recommended dose regimens and the effects of food on absorption).

Clinical experience

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 800 mg/day in divided doses was evaluated for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products in a non-comparative salvage therapy trial (Study 0041). Clinical outcomes were compared with those in an external control group derived from a retrospective review of medical records. The external control group included 86 patients treated with available therapy (as above) mostly at the same time and at the same sites as the patients treated with posaconazole. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88 %) and in the external control group (79 %).

As shown in Table 3, a successful response (complete or partial resolution) at the end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group should be viewed with caution.

Table 3. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species				
All mycologically confirmed *Aspergillus* spp.1	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 124 days and up to 212 days. Among eighteen patients who were intolerant or had infections refractory to amphotericin B or itraconazole, seven patients were classed as responders.

Chromoblastomycosis/Mycetoma
9 of 11 patients were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 268 days and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis
11 of 16 patients were successfully treated (at the end of treatment complete or partial resolution of signs and symptoms present at baseline*)* with posaconazole oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

Treatment of azole-susceptible Oropharyngeal Candidiasis (OPC)
A randomised, evaluator-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis (most patients studied had C. albicans isolated at baseline). The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both

[1] Includes other less common species or species unknown

posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical response rates from the above study are shown in the Table 4 below.
Posaconazole was shown to be non-inferior to fluconazole for clinical success rates at Day 14 as well as 4 weeks after the end of treatment.

Table 4. Clinical success rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical success rate at Day 14	91.7 % (155/169)	92.5 % (148/160)
Clinical success rate 4 weeks after end of treatment	68.5 % (98/143)	61.8 % (84/136)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. New diagnosis of acute myelogenous leukaemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 5 and 6 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 5. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	**Posaconazole oral suspension**	**Control[a]**	**P-Value**
Proportion (%) of patients with proven/probable IFIs			
On-treatment period[b]			
1899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-time period[c]			
1899[d]	14/304 (5)	33/298 (11)	0.0031

Study	Posaconazole oral suspension	Control[a]	P-Value
Proportion (%) of patients with proven/probable IFIs			
316 [d]	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
a: FLU/ITZ (1899); FLU (316).
b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

Table 6. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period[b]		
1899[d]	2/304 (1)	20/298 (7)
316[e]	3/291 (1)	17/288 (6)
Fixed-time period[c]		
1899[d]	4/304 (1)	26/298 (9)
316 [d]	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
a: FLU/ITZ (1899); FLU (316).
b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) as well as IFI-related deaths (P = 0.0209).

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Paediatric population
Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 800 mg/day in a study for invasive fungal infections (Study 0041). Based on the available data in 16 of these paediatric patients, the safety profile appears to be similar to patients ≥ 18 years of age.

Additionally, twelve patients 13-17 years of age received posaconazole oral suspension 600 mg/day for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age. In a study (Study 03579) of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the pre-specified target (Day 7 Cav between 500 ng/mL-2,500 ng/mL) (see section 5.2).

Safety and efficacy in paediatric patients below the age of 18 years have not been established.

Electrocardiogram evaluation
Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole oral suspension (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

5.2 Pharmacokinetic properties

Absorption
Posaconazole is absorbed with a median t_{max} of 3 hours (fed patients). The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg when taken with a high fat meal. No further increases in exposure were observed when doses above 800 mg daily were administered to patients and healthy volunteers. In the fasting state, AUC increased less than in proportion to dose above 200 mg. In healthy volunteers under fasting conditions, dividing the total daily dose (800 mg) into 200 mg four times daily compared to 400 mg twice daily, was shown to increase posaconazole exposure by 2.6-fold.

Effect of food on oral absorption in healthy volunteers
The absorption of posaconazole was significantly increased when posaconazole 400 mg (once daily) was administered during and immediately after the consumption of a high fat meal (~ 50 grams fat) compared to administration before a meal, with C_{max} and AUC increasing by approximately 330 % and 360 %, respectively. The AUC of posaconazole is: 4 times greater when administered with a high-fat meal (~ 50 grams fat) and about 2.6 times greater when administered during a non-fat meal or nutritional supplement (14 grams fat) relative to the fasted state (see sections 4.2 and 4.5).

Distribution
Posaconazole is slowly absorbed and slowly eliminated with a large apparent volume of distribution (1,774 litres) and is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose.

Elimination
Posaconazole is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours). After administration of ^{14}C-posaconazole, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Pharmacokinetics in special populations
Children (< 18 years)
Following administration of 800 mg per day of posaconazole as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 patients 8 - 17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was comparable among ten adolescents (13-17 years of age) to Cav achieved in adults (≥ 18 years of age). In a study of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the pre-specified

target (Day 7 Cav between 500 ng/mL-2,500 ng/mL). In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years).

Gender
The pharmacokinetics of posaconazole are comparable in men and women.

Elderly (≥ 65 years)
An increase in C_{max} (26 %) and AUC (29 %) was observed in elderly subjects (24 subjects ≥ 65 years of age) relative to younger subjects (24 subjects 18 - 45 years of age). However, in clinical efficacy trials, the safety profile of posaconazole between the young and elderly patients was similar.

Race
There was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Weight
Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg. Patients with a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment
Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal impairment (n=18, $Cl_{cr} \geq 20$ mL/min/1.73 m^2) on posaconazole pharmacokinetics; therefore, no dose adjustment is required. In subjects with severe renal impairment (n=6, Cl_{cr} < 20 mL/min/1.73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis.

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for ≥ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at systemic exposures 4.6-fold greater than the concentrations obtained at therapeutic doses in humans. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 1.4-fold greater than that achieved therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 1.4-fold and 4.6-fold greater, respectively, than those achieved with the human therapeutic doses.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Simeticone
Sodium benzoate (E211)
Sodium citrate dihydrate
Citric acid monohydrate
Glycerol
Xanthan gum
Liquid glucose
Titanium dioxide (E171)
Artificial cherry flavour containing benzyl alcohol and propylene glycol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened container: 3 years

After first opening the container: 4 weeks

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

105 mL of oral suspension in a bottle (glass amber type IV) closed with a plastic child-resistant cap (polypropylene) and a measuring spoon (polystyrene) with 2 graduations: 2.5 mL and 5 mL.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1.6.2.2.2.2　　腸溶錠

2018年7月版の添付文書を添付する。
（POS_EUSPC_NOXAFIL-TAB.pdf）

Confidential

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 100 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 100 mg of posaconazole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet (tablet)
Yellow-coated, capsule-shaped tablet of 17.5 mm length debossed with “100” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil gastro-resistant tablets are indicated for use in the treatment of the following fungal infections in adults (see section 5.1):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil gastro-resistant tablets are also indicated for prophylaxis of invasive fungal infections in the following patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

Please refer to the Summary of Product Characteristics of Noxafil oral suspension for use in oropharyngeal candidiasis.

4.2 Posology and method of administration

Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension

The tablet and oral suspension are not to be used interchangeably due to the differences between these two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Posology
Noxafil is also available as 40 mg/mL oral suspension and 300 mg concentrate for solution for infusion. Noxafil tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than Noxafil oral suspension.

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Prophylaxis of invasive fungal infections	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.

Special populations

Renal impairment
An effect of renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (see section 5.2).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil in children aged below 18 years have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

No data are available for the tablet formulation.

Method of administration
For oral use

Noxafil gastro-resistant tablets may be taken with or without food (see section 5.2). The tablets should be swallowed whole with water and should not be crushed, chewed, or broken.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see sections 4.4 and 4.5).

Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity
There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Noxafil to patients with hypersensitivity to other azoles.

Hepatic toxicity
Hepatic reactions (e.g. mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.
Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of Noxafil should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation
Some azoles have been associated with prolongation of the QTc interval. Noxafil must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Noxafil should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in section 4.3).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Drug Interactions
Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see section 4.5).

Midazolam and other benzodiazepines
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Vincristine Toxicity
Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see section 4.5).

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), and efavirenz.
Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Plasma exposure
Posaconazole plasma concentrations following administration of posaconazole tablets are generally higher than those obtained with posaconazole oral suspension. Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients (see section 5.2). Safety data at higher exposure levels achieved with posaconazole tablets are at present limited.

Gastrointestinal dysfunction
There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on posaconazole
Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux *in vitro*. Therefore, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these clearance pathways may increase or decrease posaconazole plasma concentrations, respectively.

Rifabutin
Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole to 57 % and 51 %, respectively. Concomitant use of posaconazole and rifabutin and similar inducers (e.g. rifampicin) should be avoided unless the benefit to the patient outweighs the risk. See also below regarding the effect of posaconazole on rifabutin plasma levels.

Efavirenz
Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir
Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin and similar inducers (e.g. carbamazepine, phenobarbital, primidone) should be avoided unless the benefit to the patient outweighs the risk.

H_2 receptor antagonists and proton pump inhibitors
No clinically relevant effects were observed when posaconazole tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors. No dosage adjustment of posaconazole tablets is required when posaconazole tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors.

Effects of posaconazole on other medicinal products
Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates may result in large increases in exposure to CYP3A4 substrates as exemplified by the effects on tacrolimus, sirolimus, atazanavir and midazolam below. Caution is advised during co-administration of posaconazole with CYP3A4 substrates administered intravenously and the dose of the CYP3A4 substrate may need to be reduced. If posaconazole is used concomitantly with CYP3A4 substrates that are administered orally, and for which an increase in plasma concentrations may be associated with unacceptable adverse reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions should be closely monitored and the dose adjusted as needed. Several of the interaction studies were conducted in healthy volunteers in whom a higher exposure to posaconazole occurs compared to patients administered the same dose. The effect of posaconazole on CYP3A4 substrates in patients might be somewhat lower than that observed in healthy volunteers, and is expected to be variable between patients due to the variable posaconazole exposure in patients. The effect of co-administration with posaconazole on plasma levels of CYP3A4 substrates may also be variable within a patient.

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates)
Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see section 4.3).

Ergot alkaloids
Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin)
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis (see section 4.3).

Vinca alkaloids
Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of posaconazole oral suspension (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold (range 3.1 to 17.5-fold), respectively, in healthy subjects. The effect of posaconazole on sirolimus in patients is unknown, but is expected to be variable due to the variable posaconazole exposure in patients. Co-administration of posaconazole with sirolimus is not recommended and should be avoided whenever possible. If it is considered that co-administration is unavoidable, then it is recommended that the dose of sirolimus should be greatly reduced at the time of initiation of posaconazole therapy and that there should be very frequent monitoring of trough concentrations of sirolimus in whole blood. Sirolimus concentrations should be measured upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly**.** It should be noted that the relationship between sirolimus trough concentration and AUC is changed during co-administration with posaconazole. As a result, sirolimus trough concentrations that fall within the usual therapeutic range may result in sub-therapeutic levels. Therefore, trough concentrations that fall in the upper part of the usual therapeutic range should be targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin should be adjusted as necessary.

Tacrolimus
Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

HIV Protease inhibitors
As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir (300 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 2.6-fold and 3.7-fold (range 1.2 to 26-fold),

respectively. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir and ritonavir (300/100 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 1.5-fold and 2.5-fold (range 0.9 to 4.1-fold), respectively. The addition of posaconazole to therapy with atazanavir or with atazanavir plus ritonavir was associated with increases in plasma bilirubin levels. Frequent monitoring for adverse reactions and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Midazolam and other benzodiazepines metabolised by CYP3A4
In a study in healthy volunteers posaconazole oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole oral suspension 400 mg twice daily for 7 days increased the intravenous midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, posaconazole oral suspension (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration.
Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin
Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas
Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential have to use effective contraception during treatment. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding
Posaconazole is excreted into the milk of lactating rats (see section 5.3). The excretion of posaconazole in human breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with posaconazole.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (3.4 times the 300-mg tablet based on steady-state plasma concentrations in patients) or female rats at a dose up to 45 mg/kg (2.6 times the 300-mg tablet based on steady-state plasma concentrations in patients). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Safety data mainly derive from studies with the oral suspension.

The tablet formulation was investigated in AML and MDS patients and those after HSCT with or at risk for Graft versus Host Disease (GvHD) only. Maximum duration of exposure to the tablet formulation was shorter than with the oral suspension. Plasma exposure resulting from the tablet formulation was higher than observed with the oral suspension. A higher incidence of adverse reactions cannot be ruled out.

Summary of the safety profile

Posaconazole tablets
The safety of posaconazole tablets has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole tablets when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following twice daily dosing on Day 1 in each cohort).

Posaconazole tablet and oral suspension safety
The safety of posaconazole oral suspension has been assessed in > 2,400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. The most frequently reported serious related adverse reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.
The safety of posaconazole tablet has been assessed in 336 patients and healthy volunteers enrolled in clinical trials. The safety profile of tablets was similar to that of the oral suspension.

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
Rare:	haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy, haemorrhage
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction
Endocrine disorders	
Rare:	adrenal insufficiency, blood gonadotropin decreased
Metabolism and nutrition disorders	
Common:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common:	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort

Uncommon: Rare:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth gastrointestinal haemorrhage, ileus
Hepatobiliary disorders Common: Uncommon: Rare:	 liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased) hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders Common: Uncommon: Rare:	 rash, pruritis mouth ulceration, alopecia, dermatitis, erythema, petechiae Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders Uncommon:	 back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders Uncommon: Rare:	 acute renal failure, renal failure, blood creatinine increased renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders Uncommon: Rare:	 menstrual disorder breast pain
General disorders and administration site conditions Common: Uncommon: Rare:	 pyrexia (fever), asthenia, fatigue oedema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, mucosal inflammation tongue oedema, face oedema
Investigations Uncommon:	 altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

§ See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance of posaconazole oral suspension, severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of posaconazole tablets.

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC04.

Mechanism of action
Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology
Posaconazole has been shown *in vitro* to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor*, *Mucor*, and *Rhizopus.* The microbiological data suggest that posaconazole is active against *Rhizomucor*, *Mucor*, and *Rhizopus;* however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Resistance
Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Epidemiological Cut-off (ECOFF) Values for *Aspergillus spp.*
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

Combination with other antifungal agents

The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Clinical experience

Summary of posaconazole tablet bridging study

Study 5615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole tablet. Study 5615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program. The pharmacokinetics and safety data from Study 5615 were bridged to the existing data (including efficacy data) with the oral suspension.

The subject population included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. Two different dosing groups were evaluated: 200 mg twice daily on Day 1, followed by 200 mg once daily thereafter (Part IA) and 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter (Part 1B and Part 2).

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. Moreover, sparse PK samples were collected at several days during steady state before the next dose (C_{min}) for a larger subject population. Based on average C_{min} concentrations, a predicted average concentration (Cav) could be calculated for 186 subjects dosed with 300 mg. PK analysis in patients of Cav found that 81 % of the subjects treated with the 300 mg once daily dose attained steady state predicted Cav between 500-2,500 ng/mL. One subject (<1 %) had a predicted Cav below 500 ng/mL and 19 % of the subjects had a predicted Cav above 2,500 ng/mL. Subjects achieved a mean predicted Cav at steady state of 1,970 ng/mL.

In Table 3 a comparison is shown of exposure (Cav) after administration of posaconazole tablet and posaconazole oral suspension at therapeutic doses in patients depicted as quartile analysis. Exposures after tablet administration are generally higher than, but overlapping with, exposures after administration of posaconazole oral suspension.

Table 3. Cav quartile analyses of pivotal patient studies with posaconazole tablet and oral suspension

	Posaconazole tablet	**Posaconazole oral suspension**		
	Prophylaxis in AML and HSCT Study 5615	**Prophylaxis in GVHD Study 316**	**Prophylaxis in Neutropenia Study 1899**	**Treatment - Invasive Aspergillosis Study 0041**
	300 mg once daily (Day 1 300 mg twice daily)*	**200 mg three times daily**	**200 mg three times daily**	**200 mg four times daily (hospitalized) then 400 mg twice daily**
Quartile	**pCav Range (ng/mL)**	**Cav Range (ng/mL)**	**Cav Range (ng/mL)**	**Cav Range (ng/mL)**
Q1	442 – 1,223	22 – 557	90 – 322	55 – 277
Q2	1,240 – 1,710	557 – 915	322 – 490	290 – 544
Q3	1,719 – 2,291	915 – 1,563	490 – 734	550 – 861
Q4	2,304 – 9,523	1,563 – 3,650	734 – 2,200	877 – 2,010

pCav: predicted Cav
Cav = the average concentration when measured at steady state
*20 patients received 200 mg once daily (Day 1 200 mg twice daily)

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 800 mg/day in divided doses was evaluated for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products in a non-comparative salvage therapy trial (Study 0041). Clinical outcomes were compared with those in an external control group derived from a retrospective review of medical records. The external control group included 86 patients treated with available therapy (as above) mostly at the same time and at the same sites as the patients treated with posaconazole. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88 %) and in the external control group (79 %).
As shown in Table 4, a successful response (complete or partial resolution) at the end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group should be viewed with caution.

Table 4. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species				
All mycologically confirmed *Aspergillus* spp.[2]	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 124 days and up to 212 days. Among eighteen patients who were intolerant or had infections refractory to amphotericin B or itraconazole, seven patients were classed as responders.

Chromoblastomycosis/Mycetoma
9 of 11 patients were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 268 days and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis
11 of 16 patients were successfully treated (at the end of treatment complete or partial resolution of signs and symptoms present at baseline*)* with posaconazole oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent,

[2] Includes other less common species or species unknown

blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. New diagnosis of acute myelogenous leukaemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 5 and 6 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 5. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]	P-Value
Proportion (%) of patients with proven/probable IFIs			
On-treatment period[b]			
1899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-time period[c]			
1899[d]	14/304 (5)	33/298 (11)	0.0031
316[d]	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.

c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.

d: All randomized

e: All treated

Table 6. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period[b]		
1899[d]	2/304 (1)	20/298 (7)
316[e]	3/291 (1)	17/288 (6)
Fixed-time period[c]		
1899[d]	4/304 (1)	26/298 (9)
316[d]	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.

c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.

d: All randomized

e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) as well as IFI-related deaths (P = 0.0209).

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Paediatric population

There is no paediatric experience for posaconazole tablets.

Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 800 mg/day in a study for invasive fungal infections. Based on the available data in 16 of these paediatric patients, the safety profile appears to be similar to patients ≥ 18 years of age.

Additionally, twelve patients 13-17 years of age received posaconazole oral suspension 600 mg/day for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

Safety and efficacy in paediatric patients below the age of 18 years have not been established.

Electrocardiogram evaluation

Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole oral suspension (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

5.2 Pharmacokinetic properties

Pharmacokinetic / Pharmacodynamic relationships

A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is

particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see sections 4.2 and 5.2 on recommended dose regimens).

Absorption
Posaconazole tablets are absorbed with a median T_{max} of 4 to 5 hours and exhibits dose proportional pharmacokinetics after single and multiple dosing up to 300 mg.

Following a single dose administration of 300 mg posaconazole tablets after a high fat meal to healthy volunteers, the $AUC_{0\text{-}72\ hours}$ and C_{max} were higher compared to administration under fasted condition (51 % and 16 % for $AUC_{0\text{-}72\ hours}$ and C_{max} respectively).

Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients. The reason for this time-dependency is not completely understood.

Distribution
Posaconazole, after administration of the tablet, has a mean apparent volume of distribution of 394 L (42 %), ranging between 294-583 L among the studies in healthy volunteers.

Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose.

Elimination
Posaconazole after administration of the tablets, is slowly eliminated with a mean half-life ($t_{½}$) of 29 hours (range 26 to 31 hours) and a mean apparent clearance ranging from 7.5 to 11 L/hr. After administration of ^{14}C-posaconazole, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Pharmacokinetics in special populations
Children (< 18 years)
There is no paediatric experience with posaconazole tablets.
The pharmacokinetics of posaconazole oral suspension have been evaluated in paediatric patients. Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 patients 8 - 17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). No pharmacokinetic data are available from paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was comparable among ten adolescents (13-17 years of age) to Cav achieved in adults (≥ 18 years of age).

Gender
The pharmacokinetics of posaconazole tablets are comparable in men and women.

Elderly
The pharmacokinetics of posaconazole tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race
There is insufficient data among different races with posaconazole tablets.

There was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Weight
Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Patients, in particular those receiving posaconazole after HSCT, who have a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment
Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal impairment (n=18, $Cl_{cr} \geq 20$ mL/min/1.73 m^2) on posaconazole pharmacokinetics; therefore, no dose adjustment is required. In subjects with severe renal impairment (n=6, Cl_{cr} < 20 mL/min/1.73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis.

Similar recommendations apply to posaconazole tablets; however, a specific study has not been conducted with the posaconazole tablets.

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

Similar recommendations apply to posaconazole tablets; however, a specific study has not been conducted with the posaconazole tablets.

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for ≥ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at maximal plasma concentrations 8.5-fold greater than the concentrations obtained at therapeutic doses in humans. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 2.1-fold greater than that achieved therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 2.1-fold and 8.5-fold greater, respectively, than those achieved with the human therapeutic doses.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose acetate succinate
Cellulose, microcrystalline
Hydroxypropylcellulose (E463)
Silica dental type
Croscarmellose sodium
Magnesium stearate

Tablet coat
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc
iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Noxafil 100 mg gastro-resistant tablets are packaged in a PVC/ polychlorotrifluoroethylene laminate blister with push-through aluminium lidding.

Noxafil gastro-resistant tablets are packaged in a blister in cartons of 24 (2x12) or 96 (8x12) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/002	24 tablets
EU/1/05/320/003	96 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1.6.2.2.2.3　　静注用濃厚溶液

2018年7月版の添付文書を添付する。
（POS_EUSPC_NOXAFIL-IV.pdf）

Confidential

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of posaconazole.
Each mL contains 18 mg of posaconazole.

Excipient with known effect:
Each vial contains 462 mg (20 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil concentrate for solution for infusion is indicated for use in the treatment of the following fungal infections in adults (see section 5.1):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil concentrate for solution for infusion is also indicated for prophylaxis of invasive fungal infections in the following patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease (GVHD) and who are at high risk of developing invasive fungal infections.

Please refer to the Summary of Product Characteristics of Noxafil oral suspension for use in oropharyngeal candidiasis.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Posology
Noxafil is also available for oral administration (Noxafil 100 mg gastro-resistant tablets and 40 mg/mL oral suspension). A switch to oral administration is recommended as soon as the patients' condition allows (see section 4.4).

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg Noxafil twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Prophylaxis of invasive fungal infections	Loading dose of 300 mg Noxafil twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or MDS, prophylaxis with Noxafil should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.

Noxafil should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Noxafil concentrate for solution for infusion should not be given by bolus administration. If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes (see section 4.8 and 6.6).

Special populations

Renal impairment
In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Oral formulations of Noxafil should be used in these patients unless an assessment of the benefit/risk to the patient justifies the use of Noxafil concentrate for solution for infusion. Serum creatinine levels should be closely monitored in these patients (see section 4.4).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil concentrate for solution for infusion in children aged below 18 years have not been established.
No data are available.

Noxafil concentrate for solution for infusion should not be used in children aged below 18 years because of pre-clinical safety concerns (see section 5.3).

Method of administration
Noxafil concentrate for solution for infusion requires dilution (see section 6.6) prior to administration. Noxafil should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes (see sections 4.2, 4.4, and 4.8).
Noxafil concentrate for solution for infusion should not be given by bolus administration.

If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes to reduce the likelihood of infusion site reactions (see section 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see sections 4.4 and 4.5).

Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity
There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Noxafil to patients with hypersensitivity to other azoles.

Hepatic toxicity
Hepatic reactions (e.g. elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.

Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of patients with severe renal impairment
Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin).

Discontinuation of Noxafil should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation
Some azoles have been associated with prolongation of the QTc interval. Noxafil must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Noxafil should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in section 4.3).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.
In patients, mean maximum plasma concentrations (C_{max}) after posaconazole concentrate for solution for infusion are 4-fold increased compared to administration of oral suspension. An increased effect on the QTc interval cannot be ruled out. Particular caution is advised in such cases where posaconazole is administered peripherally, as the recommended infusion time of 30 minutes may further increase C_{max}.

Drug Interactions
Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see section 4.5).

Midazolam and other benzodiazepines
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Vincristine toxicity
Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see section 4.5).

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), and efavirenz
Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Plasma exposure
Plasma concentrations following administration of posaconazole intravenous concentrate for solution for infusion are generally higher than those obtained with posaconazole oral suspension.
Posaconazole plasma concentrations following administration of posaconazole may increase over time in some patients (see section 5.2). Safety data at higher exposure levels achieved with posaconazole concentrate for solution for infusion are at present limited.

Thromboembolic events
Thromboembolic events have been identified as a potential risk for posaconazole intravenous concentrate for solution for infusion but were not observed in the clinical studies. Thrombophlebitis

was observed in clinical trials. Caution is warranted on any sign or symptom of thromboembolic events (see sections 4.8 and 5.3).

Sodium content
Each vial of Noxafil contains 462 mg (20 mmol) of sodium. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following information was derived from data with posaconazole oral suspension or early tablet formulation. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole concentrate for solution for infusion as well.

Effects of other medicinal products on posaconazole
Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux *in vitro*. Therefore, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these clearance pathways may increase or decrease posaconazole plasma concentrations, respectively.

Rifabutin
Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole to 57 % and 51 %, respectively. Concomitant use of posaconazole and rifabutin and similar inducers (e.g. rifampicin) should be avoided unless the benefit to the patient outweighs the risk. See also below regarding the effect of posaconazole on rifabutin plasma levels.

Efavirenz
Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir
Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin and similar inducers (e.g. carbamazepine, phenobarbital, primidone) should be avoided unless the benefit to the patient outweighs the risk.

Effects of posaconazole on other medicinal products
Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates may result in large increases in exposure to CYP3A4 substrates as exemplified by the effects on tacrolimus, sirolimus, atazanavir and midazolam below. Caution is advised during co-administration of posaconazole with CYP3A4 substrates administered intravenously and the dose of the CYP3A4 substrate may need to be reduced. If posaconazole is used concomitantly with CYP3A4 substrates that are administered orally, and for which an increase in plasma concentrations may be

associated with unacceptable adverse reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions should be closely monitored and the dose adjusted as needed.

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates)
Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see section 4.3).

Ergot alkaloids
Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin)
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis (see section 4.3).

Vinca alkaloids
Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
After oral administration, posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of oral posaconazole oral suspension (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold (range 3.1 to 17.5-fold), respectively, in healthy subjects. The effect of posaconazole on sirolimus in patients is unknown, but is expected to be variable due to the variable posaconazole exposure in patients. Co-administration of posaconazole with sirolimus is not recommended and should be avoided whenever possible. If it is considered that co-administration is unavoidable, then it is recommended that the dose of sirolimus should be greatly reduced at the time of initiation of posaconazole therapy and that there should be very frequent monitoring of trough concentrations of sirolimus in whole blood. Sirolimus concentrations should be measured upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly**.** It should be noted that the relationship between sirolimus trough concentration and AUC is changed during co-administration with posaconazole. As a result, sirolimus trough concentrations that fall within the usual therapeutic range may result in sub-therapeutic levels. Therefore trough concentrations that fall in the upper part of the usual therapeutic range should be targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin

levels resulting in serious adverse reactions, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin should be adjusted as necessary.

Tacrolimus
Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

HIV Protease inhibitors
As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir (300 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 2.6-fold and 3.7-fold (range 1.2 to 26-fold), respectively. Following co-administration of posaconazole oral suspension (400 mg twice daily) with atazanavir and ritonavir (300/100 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 1.5-fold and 2.5-fold (range 0.9 to 4.1-fold), respectively. The addition of posaconazole to therapy with atazanavir or with atazanavir plus ritonavir was associated with increases in plasma bilirubin levels. Frequent monitoring for adverse reactions and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Midazolam and other benzodiazepines metabolised by CYP3A4
In a study in healthy volunteers posaconazole oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole oral suspension 400 mg twice daily for 7 days increased the intravenous midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, posaconazole oral suspension (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration.
Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin
Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas
Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential have to use effective contraception during treatment. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Breast-feeding
Posaconazole is excreted into the milk of lactating rats (see section 5.3). The excretion of posaconazole in human breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with posaconazole.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (2.8 times the exposure achieved from a 300 mg intravenous dose in human) or female rats at a dose up to 45 mg/kg (3.4 times the exposure from a 300 mg intravenous dose in patients). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Safety data mainly derive from studies with the oral suspension.

Noxafil concentrate for solution for infusion was investigated in AML and MDS patients and those after HSCT with or at risk for GVHD only. Maximum duration of exposure to the concentrate for solution for infusion was shorter than with the oral suspension. Plasma exposure resulting from the solution for infusion was higher than observed with the oral suspension. A higher incidence of adverse reactions cannot be ruled out.

Summary of the safety profile

Posaconazole concentrate for solution for infusion safety
In initial studies of healthy volunteers, administration of a single dose of posaconazole infused over 30 minutes via a peripheral venous catheter was associated with a 12 % incidence of infusion site reactions (4 % incidence of thrombophlebitis). Multiple doses of posaconazole administered via a peripheral venous catheter were associated with thrombophlebitis (60 % incidence). Therefore, in subsequent studies posaconazole was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter. Peripheral infusion time longer than 30 minutes, leads to a higher incidence of infusion site reactions and thrombophlebitis.

The safety of posaconazole concentrate for solution for infusion has been assessed in 268 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole concentrate for solution for infusion when given as antifungal prophylaxis (Study 5520). Eleven patients received a single dose of 200 mg posaconazole concentrate for solution for infusion, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. No safety data are available for administration > 28 days. Safety data in the elderly are limited.

The most frequently reported adverse reaction (>25 %) with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily was diarrhoea (32 %).

The most common adverse reaction (>1 %) leading to discontinuation of posaconazole concentrate for solution for infusion 300 mg once daily was AML (1 %).

Tabulated list of adverse reactions

Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
Rare:	haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy, haemorrhage
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction
Endocrine disorders	
Rare:	adrenal insufficiency, blood gonadotropin decreased
Metabolism and nutrition disorders	
Common:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	Hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment

Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, thrombophlebitis, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
Rare:	gastrointestinal haemorrhage, ileus
Hepatobiliary disorders	
Common:	liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased)
Uncommon:	hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	breast pain
General disorders and administration site conditions	
Common:	pyrexia (fever), asthenia, fatigue
Uncommon:	oedema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, infusion site pain, infusion site phlebitis, infusion site thrombosis, mucosal inflammation
Rare:	tongue oedema, face oedema

Investigations Uncommon:	altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.
§ See section 4.4.

Description of selected adverse reactions
Hepatobiliary disorders
During post-marketing surveillance severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of posaconazole concentrate for solution for infusion.

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C04.

Mechanism of action
Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology
Posaconazole has been shown *in vitro* to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor*, *Mucor*, and *Rhizopus.* The microbiological data suggest that posaconazole is active against *Rhizomucor*, *Mucor*, and *Rhizopus;* however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Resistance
Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Epidemiological Cut-off (ECOFF) values for *Aspergillus spp*.
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

Combination with other antifungal agents
The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Clinical experience

Summary of posaconazole concentrate for solution for infusion bridging study
Study 5520 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole concentrate for solution for infusion.

Study 5520 enrolled a total of 279 subjects, including 268 receiving at least one dose of posaconazole concentrate for solution for infusion. Cohort 0 was designed to evaluate the tolerability of a single dose of posaconazole concentrate for solution for infusion when administered via a central line. The subject population for Cohorts 1 and 2 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Cohorts 1 and 2: 200 mg twice daily on Day 1, followed by 200 mg once daily thereafter (Cohort 1) and 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter (Cohort 2).

The subject population in Cohort 3 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Cohorts 1 and 2, all subjects in Cohort 3 received 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter.

The total subject population had a mean age of 51 years (range = 18-82 years), 95 % were White, the major ethnicity was not Hispanic or Latino (92 %), and 55 % were male. The study treated 155 (65 %) subjects with AML or MDS, and 82 (35 %) subjects with HSCT, as the primary diseases at study entry.

Serial pharmacokinetic samples were collected on Day 1 and at steady-state on Day 14 for all Cohort 1 and 2 subjects and on Day 10 for a subset of Cohort 3 subjects. This serial pharmacokinetic analysis demonstrated that 94 % of the subjects treated with the 300 mg once daily dose attained steady state Cav between 500-2500 ng/mL [Cav was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).]. This exposure was selected based on pharmacokinetic/pharmacodymanic considerations with posaconazole oral suspension. Subjects who received 300 mg once daily achieved a mean Cav at steady state of 1500 ng/mL.

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 800 mg/day in divided doses was evaluated for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products in a non-comparative salvage therapy trial. Clinical outcomes were compared with those in an external control group derived from a retrospective review of medical records. The external control group included 86 patients treated with available therapy (as above) mostly at the same time and at the same sites as the patients treated with posaconazole. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88 %) and in the external control group (79 %).

As shown in Table 3, a successful response (complete or partial resolution) at the end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group should be viewed with caution.

Table 3. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species				
All mycologically confirmed *Aspergillus* spp.[3]	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 124 days and up to 212 days. Among eighteen patients who were intolerant or had infections refractory to amphotericin B or itraconazole, seven patients were classed as responders.

Chromoblastomycosis/Mycetoma
9 of 11 patients were successfully treated with posaconazole oral suspension 800 mg/day in divided doses for a median of 268 days and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis
11 of 16 patients were successfully treated (at the end of treatment complete or partial resolution of signs and symptoms present at baseline*)* with posaconazole oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

[3] Includes other less common species or species unknown

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. New diagnosis of acute myelogenous leukaemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 4 and 5 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 4. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]	P-Value
Proportion (%) of patients with proven/probable IFIs			
On-treatment period[b]			
1899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-time period[c]			
1899[d]	14/304 (5)	33/298 (11)	0.0031
316 [d]	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
a: FLU/ITZ (1899); FLU (316).
b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

Table 5. Results from clinical studies in prophylaxis of Invasive Fungal Infections

Study	Posaconazole oral suspension	Control[a]
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period[b]		
1899[d]	2/304 (1)	20/298 (7)
316[e]	3/291 (1)	17/288 (6)
Fixed-time period[c]		
1899[d]	4/304 (1)	26/298 (9)
316[d]	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
a: FLU/ITZ (1899); FLU (316).
b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) as well as IFI-related deaths (P = 0.0209).

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Paediatric population
There is no paediatric experience for posaconazole concentrate for solution for infusion.

Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 800 mg/day in a study for invasive fungal infections. Based on the available data in 16 of these paediatric patients, the safety profile appears to be similar to patients ≥ 18 years of age.

Additionally, twelve patients 13-17 years of age received posaconazole oral suspension 600 mg/day for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

Safety and efficacy in paediatric patients below the age of 18 years have not been established.

Electrocardiogram evaluation
Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole oral suspension (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

5.2 Pharmacokinetic properties

Pharmacokinetic / Pharmacodynamic relationships
A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is

particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see sections 4.2 and 5.2 on recommended dose regimens).

Distribution
Following administration of 300 mg posaconazole concentrate for solution for infusion over 90 minutes, mean peak plasma concentration at the end of infusion was 3280 ng/mL (74 % CV). Posaconazole exhibits dose proportional pharmacokinetics after single and multiple dosing in the therapeutic dose range (200-300 mg). Posaconazole has a distribution volume of 261 L, indicating extravascular distribution.

Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose of posaconazole oral suspension.

Elimination
Posaconazole, after administration of 300 mg of posaconazole concentrate for solution for infusion, is slowly eliminated with a mean half-life ($t_{½}$) of 27 hours and a mean clearance of 7.3 L/hr. After administration of ^{14}C-posaconazole as oral suspension, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Posaconazole plasma concentrations following administration of posaconazole concentrate for solution for infusion single dose increased in a greater than dose proportional manner over the range of 50-200 mg; by comparison, dose-dependent increases were observed over a range of 200-300 mg.

Pharmacokinetics in special populations
Children (< 18 years)
There is no paediatric experience with posaconazole concentrate for solution for infusion (see sections 4.2 and 5.3).

Gender
The pharmacokinetics of posaconazole concentration for solution for infusion are comparable in men and women.

Elderly
The pharmacokinetics of posaconazole concentrate for solution for infusion are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race
There is insufficient data among different races with posaconazole concentrate for solution for infusion.

There was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Weight
Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg. Patients with a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment
Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal impairment (n=18, $Cl_{cr} \geq 20$ mL/min/1.73 m^2) on posaconazole pharmacokinetics; therefore, no dose adjustment is required. In subjects with severe renal impairment (n=6, Cl_{cr} < 20 mL/min/1.73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see section 4.2).

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for ≥ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at maximal plasma concentrations 8.9-fold greater than the concentrations obtained at therapeutic doses in humans with 300 mg intravenous infusion administration. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 2.2-fold greater than that achieved

therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 2.2-fold and 8.9-fold greater, respectively, than those achieved with the human therapeutic doses.

A non-dose related incidence of thrombus/emboli in the lung was seen in the 1 month repeated dose study in the monkey. The clinical significance of this finding is unknown.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2-8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioural or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). The clinical significance of this finding is unknown; therefore, the use of posaconazole concentrate for solution for infusion to patients under 18 years of age is not recommended (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium (SBECD)
Disodium edetate
Hydrochloric acid [for pH adjustment]
Sodium hydroxide [for pH adjustment]
Water for injections

6.2 Incompatibilities

Noxafil must not be diluted with:

Lactated Ringer’s solution
5 % dextrose with Lactated Ringer’s solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

From a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2°C-8°C. This medicinal product is for single use only.

6.4 Special precautions for storage

Store in a refrigerator at 2°C-8°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial closed with bromobutyl rubber stopper and aluminium seal containing 16.7 mL of solution.
Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Administration instructions for Noxafil concentrate for solution for infusion

- Equilibrate the refrigerated vial of Noxafil to room temperature.
- Aseptically transfer 16.7 mL of posaconazole to an intravenous bag (or bottle) containing a compatible admixture diluent (see below for list of diluents) using the volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Noxafil concentrate for solution for infusion should not be given by bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter with a volume to achieve a dilution of approximately 2 mg/mL. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes.
  Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions (see section 4.8).
- Noxafil is for single use.

The following medicinal products can be infused at the same time through the same intravenous line (or cannula) as Noxafil concentrate for solution for infusion:

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulphate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Any products not listed in the table above should not be coadministered with Noxafil through the same intravenous line (or cannula).

Noxafil concentrate for solution for infusion should be inspected visually for particulate matter prior to administration. The solution of Noxafil ranges from colourless to pale yellow. Variations of colour within this range do not affect the quality of the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Noxafil must not be diluted with:

Lactated Ringer's solution
5 % dextrose with Lactated Ringer's solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned below:

5 % dextrose in water
0.9 % sodium chloride
0.45 % sodium chloride
5 % dextrose and 0.45 % sodium chloride
5 % dextrose and 0.9 % sodium chloride
5 % dextrose and 20 mEq KCl

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/004 1 vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1.6.2.2.3　　オーストラリア添付文書（原文）

1.6.2.2.3.1　　経口懸濁液及び徐放錠

2017年9月版の添付文書を添付する。

（Australia_POS_TAB_Oral-Sus_20170929.pdf）

Confidential

Product Information

NOXAFIL®

(posaconazole)

MODIFIED RELEASE 100 mg TABLETS

and 40 mg/mL ORAL SUSPENSION

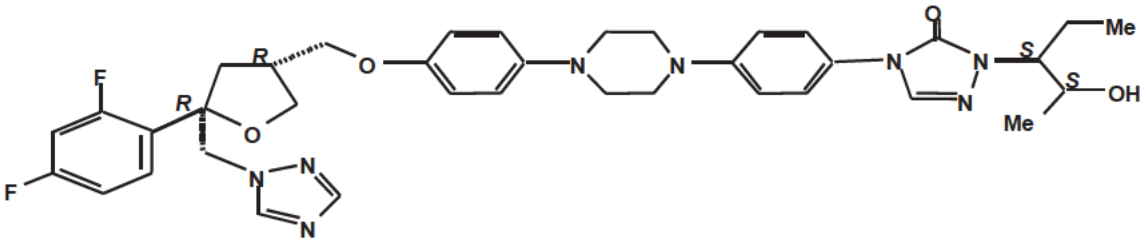
NAME OF THE MEDICINE

Posaconazole.

Posaconazole is a broad spectrum triazole antifungal compound with a molecular formula of $C_{37}H_{42}F_2N_8O_4$ yielding a molecular weight of 700.8.

The chemical structure, which possesses four chiral centres, two R and two S, and chemical name are illustrated below:

SCH 56592 (Posaconazole)



CAS INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydropropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)

CAS RN 171228-49-2.

IUPAC NAME: 4-4-[4-(4-{(3R, 5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one.

DESCRIPTION

Posaconazole is a white to off-white crystalline powder. It has a melting range of 164° C – 165°C and is insoluble in water.

NOXAFIL ORAL SUSPENSION is a white, cherry flavoured immediate-release oral suspension containing 40 mg of posaconazole per mL.

List of excipients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavouring, and purified water.

NOXAFIL MODIFIED RELEASE TABLET is a yellow, coated, capsule-shaped tablet containing 100 mg of posaconazole.

List of excipients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol, Macrogol 3350, titanium dioxide, purified talc, and iron oxide yellow).

PHARMACOLOGY

Pharmacodynamic properties

Antiinfective for systemic use, triazole derivative, J02AC04

Mechanism of action:

Posaconazole is a triazole antifungal agent. It is an inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Ergosterol depletion, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and the function of some membrane-associated proteins. This results in the inhibition of cell growth and/or cell death.

Microbiology:

Posaconazole has been shown *in vitro* and in clinical infections to be active against the following micro-organisms: (See Indications): *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus, A. ochraceus*), *Candida* species (*Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Fonsecaea pedrosoi*, *Histoplasma capsulatum, Pseudallescheria boydii* and species of *Alternaria*, *Exophiala*, *Fusarium*, *Ramichloridium, Rhizomucor*, *Mucor*, and *Rhizopus).* While posaconazole has been used in a clinical setting against these microorganisms, sufficient evidence for efficacy has not been collected for all the listed microorganisms (see Clinical Trials).

Posaconazole also exhibits in vitro activity against the following yeasts and moulds: *Candida dubliniensis, C. famata, C. guilliermondii, C. lusitaniae, C. kefyr, C. rugosa, C. tropicalis, C. zeylanoides, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis, Cryptococcus laurentii, Kluyveromyces marxianus, Saccharomyces cerevisiae, Yarrowia lipolytica,* species of *Pichia,* and *Trichosporon, Aspergillus sydowii, Bjerkandera adusta, Blastomyces dermatitidis, Epidermophyton floccosum, Paracoccidioides brasiliensis, Scedosporium apiospermum, Sporothrix schenckii, Wangiella dermatitidis* and species of *Absidia, Apophysomyces, Bipolaris, Curvularia, Microsporum, Paecilomyces, Penicillium*, and *Trichophyton*. However, the safety and effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

NOXAFIL exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole,
- *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole,
- *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B)
- organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g. species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*).

In vitro NOXAFIL exhibited fungicidal activity against species of:

- *Aspergillus*,

- dimorphic fungi (*Blastomyces dermatitidis, Histoplasma capsulatum, Penicillium marneffei,*
- *Coccidioides immitis*)
- some species of *Candida*.

In animal infection models NOXAFIL was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Drug Resistance:

C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of $1x10^{-8}$ to $1x10^{-9}$. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active in vitro against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal drug combinations:

When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. Clinical studies of posaconazole in combination with antifungal drugs including amphotericin B-based drugs and caspofungin have not been conducted.

Pharmacokinetic Properties

Absorption:

Posaconazole oral suspension is absorbed with a median T_{max} of 3 hours (patients) and ~ 5 hours (healthy volunteers). Intersubject variability in mean AUC and C_{max} was high in healthy volunteers and patients despite the controlled conditions in pharmacokinetic studies. Steady-state is attained following 7 to 10 days of multiple-dose administration.

The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure are observed above a total daily dose of 800 mg in patients and healthy volunteers. There is no effect of altered pH on the absorption of posaconazole (See Drug Interactions).

Dividing the total posaconazole daily dose (800 mg) as 400 mg twice a day results in a 184 % higher exposure relative to once-a-day administration in patients. Exposure further increased when posaconazole was given as 200 mg four times daily.

When given orally in healthy volunteers, posaconazole modified release tablets are absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BD loading dose at Day 1).

The absolute bioavailability of the oral modified release tablet is approximately 54%.

Relative bioavailability was investigated between the 100 mg modified release tablet under fasted conditions and the 100 mg oral suspension under fed conditions in healthy adults. Under these conditions, plasma exposure to posaconazole for the two treatments was similar. Under fasted conditions, the exposure of posaconazole after single-dose modified release tablet administration was 3.7-fold higher than the oral suspension.

Effect of food on oral absorption in healthy volunteers:

The AUC of posaconazole oral suspension is about 2.6 times greater when administered with a nonfat meal or nutritional supplement (14 g fat) and 4 times greater when administered with a high-fat meal (~ 50 g fat) relative to the fasted state. Posaconazole oral suspension should be administered with food or a nutritional supplement (See Dosage and Administration).

In a single dose study (P112) investigating the effect of a high fat meal on the bioavailability of posaconazole following administration of NOXAFIL tablets 300 mg (3 x 100 mg) in healthy volunteers, the C_{max} was 16% higher and the $AUC_{0\text{-}72\ hours}$ was 51% higher with food relative to fasting. The results of the study are summarised below in Table 1. The effect of food on the absorption of NOXAFIL modified release tablets is not considered clinically meaningful. Food effect was taken into consideration at the time of final dose selection of the 300 mg modified release tablet based on data from the pivotal clinical Phase 1b/Phase 3 pharmacokinetic/safety study P5615 in which patients took NOXAFIL modified release tablets without regard to food intake. NOXAFIL modified release tablets can therefore be administered with or without food.

Table 1: Statistical comparison of plasma pharmacokinetics of Posaconazole following single oral dose administration of 300 mg Posaconazole (as 3 tablets of 100 mg) to healthy subjects under fasting and fed conditions

	Fasting Conditions		**Fed Conditions** (High Fat Meal)*		**Fed/Fasting**
Pharmacokinetic Parameter	**N**	**GM (95% CI)**	**N**	**GM (95% CI)**	**GMR (90% CI)**
C_{max}† (ng/mL)	14	893 (731, 1090)	16	1,040 (915, 1180)	1.16 (0.96, 1.41)
$AUC_{0\text{-}last}$‡ hr·ng/mL	14	25600 (21500, 30400)	16	38700 (35000, 42700)	1.51 (1.33, 1.72)
T_{max}§ (hr)	14	5.00 (3.00, 8.00)	16	6.0 (5.00, 24.00)	N/A

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio;

CI = Confidence interval

* 48.5 g fat

†C_{max} = maximum observed concentration

‡$AUC_{0\text{-}last}$ = $AUC_{0\text{-}72hr}$

§Median (Min, Max) reported for T_{max}

Distribution:

Posaconazole oral suspension has a large apparent volume of distribution (1774 L) suggesting extensive penetration into the peripheral tissues. Posaconazole is highly protein bound (> 98.0 %), predominantly to serum albumin.

Posaconazole, after administration of the modified release tablet, has a mean apparent volume of distribution of 394 L (42% CV), ranging between 294-583 L among the studies in healthy volunteers.

Metabolism:

Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radio-labelled dose.

Excretion:

Posaconazole oral suspension is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours) and apparent total body clearance (Cl/F) of 32 L/hr.

Posaconazole modified release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

Posaconazole is predominantly excreted in the faeces (77 % of the radio-labelled dose) with the major component eliminated as parent drug (66 % of the radio-labelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radio-labelled dose excreted in urine (< 0.2 % of the radio-labelled dose is parent drug). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Summary of the mean pharmacokinetic parameters in patients:

The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent in that posaconazole oral suspension was slowly absorbed and slowly eliminated with an extensive volume of distribution. In addition, the phenomenon of dose-limited absorption of posaconazole at 800 mg/day was observed both in healthy volunteers and patients. The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole 400 mg twice a day for 7 days are displayed in Table 2.

The exposure to posaconazole oral suspension following administration of 400 mg twice a day was ~ 3 times higher in healthy volunteers than in patients, without additional safety findings at the higher concentrations (Table 2).

Table 2: Pharmacokinetics of posaconazole oral suspension in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC(τ) (ng·hr/mL)
Healthy Volunteers	400 mg twice a day (n=174)	2850 (36)	5 (0-12)	29453 (37)
Patients	400 mg twice a day (n=24)	851 (82)	3 (0-12.5)	8619 (86)

[a]Median (range)

The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole modified release tablet 300 mg daily are displayed in Table 3a. Patients have approximately 25% lower exposure as compared to healthy volunteers after multiple dosing of posaconazole modified release tablet. The differences in exposure between healthy volunteers and patients are much less than the exposure differences reported for posaconazole oral suspension (Table 2).

Table 3a: Pharmacokinetics of posaconazole modified release tablets in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC(τ) (ng·hr/mL)
Healthy Volunteers	300 mg/day (n=12)	2764 (21)	3.98 (3 - 6)	51618 (25)
Patients	300 mg/day (n=50)	2090 (38)	4 (1.3 - 8.1)	37900 (42)

Simulation based on the population pharmacokinetic model was performed in patients receiving posaconazole modified release tablet 300 mg daily (following 300 mg BD on Day 1). Simulated pharmacokinetics in patients and subpopulations of AML/MDS and HSCT patients are displayed in Table 3b.

Table 3b: Simulated multiple dose pharmacokinetics of posaconazole modified release tablets by patient sub population

Patient sub population	Dose	Mean (%CV)	
		AUC(τ) (ng·hr/mL)	C_{avg} (ng/mL)
AML/MDS	300 mg/day (n=1000)	40031 (53)	1668 (53)
HSCT*	300 mg/day (n=1000)	47307 (53)	1971 (53)
Total	300 mg/day (n=2000)	43669 (54)	1820 (54)

n= number of simulated patients; AUC(τ): Area under the concentration versus time curve during a dosing interval τ at steady state: C_{avg}: AUC(τ)τ.

*In the population PK model developed for POS modified release tablet, HSCT patients were considered not different from the healthy volunteer population.

Coadministration of food, or medications known to alter gastric pH (antacid, ranitidine, esomeprazole) or motility (metoclopramide) shows no clinically meaningful effect on the pharmacokinetics of posaconazole when administered as a modified release tablet.

In Table 4 a comparison is shown of exposure (C_{avg}) in patients after administration of posaconazole modified release tablet and posaconazole oral suspension at therapeutic doses.

Table 4: Mean C_{avg} exposure at steady state from pivotal patient studies with Posaconazole modified release tablet and Posaconazole oral suspension

	Posaconazole modified release tablet	**Posaconazole oral suspension**		
	Prophylaxis in AML and HSCT	Prophylaxis in GVHD	Prophylaxis in Neutropenia	Treatment - Invasive Aspergillosis
Study	P05615	C98-316	P01899	P00041
Dose	300 mg QD	200 mg TDS	200 mg TDS	POS 200 mg QID (hospitalized) then 400 mg BD
Mean C_{avg} (ng/mL) (%CV)	=1970 (56%)*	1122 (67%)	583 (65%)	841 (83%)
Quartile	pC_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)
Q1	442-1223	22-557	90-332	55-277
Response	N/A	55.6%	45.3%	24%

	Posaconazole modified release tablet	Posaconazole oral suspension		
	Prophylaxis in AML and HSCT	Prophylaxis in GVHD	Prophylaxis in Neutropenia	Treatment - Invasive Aspergillosis
Quartile	pC_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)
Q2	1240-1710	557-915	322-490	290-544
Response	N/A	79.4%	63.0%	53%
Q3	1719-2291	915-1563	490-734	550-861
Response	N/A	82.5%	53.7%	53%
Q4	2304-9523	550-861	734-2200	877-2010
Response	N/A	53%	72.2%	71%

mean C_{avg} = the average concentration when measured at steady state

*pC_{avg} = predicted C_{avg}

Pharmacokinetics in Special Populations:

Paediatric

Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 paediatric patients 8 - 17 years of age (776 ng /mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). No pharmacokinetic data are available from paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (C_{avg}) was comparable among ten adolescents (13 – 17 years of age) to C_{avg} achieved in adults (≥ 18 years of age).

Mean average steady-state plasma concentration was calculated for neutropenic paediatric patients aged between 11 months and 17 years treated with 12 mg/kg/day or 18 mg/kg/day of posaconazole oral suspension in two or three divided doses. Approximately 50% met the pre-specified target (Day 7 C_{avg} of 1200 ng/mL with acceptable range 500 ng/mL to 2500 ng/mL); 43% (30/70) of subjects fell below 500 ng/mL. In general, exposures tended to be closer to the target Day 7 C_{avg} in the older patients (7 to <18 years n = 36) than in younger patients (2 to <7 years; n = 33 and 3 to 23 months n = 1). (See INDICATIONS, DOSAGE AND ADMINISTRATION and PRECAUTIONS Paediatric Use)

Gender

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Elderly

Results from a multiple dose study of posaconazole oral suspension in healthy volunteers (N=48) indicated that at steady state, there was an increase in C_{max} (26 %) and AUC (29 %) observed in elderly subjects (24 subjects ≥65 years of age)

relative to younger subjects (24 subjects 18 - 45 years of age). A similar trend was observed in the clinical program based on a small proportion of elderly subjects ≥65 years of age (N=25 vs. 194 patients 18 – 64 years of age). However, in a population pharmacokinetic analysis (Study 1899), age did not influence the pharmacokinetics of posaconazole oral suspension. The safety profile of posaconazole oral suspension between the young and elderly patients was similar. Therefore no dose adjustment is required for age.

Race

Results from a multiple dose study in healthy volunteers (n = 56) indicated that there was only a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

Renal impairment

Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (eGFR: 50-80 mL/min/1.73 m^2, n=6) or moderate (eGFR: 20-49 mL/min/1.73 m^2, n=6) renal impairment on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal impairment (eGFR: < 20 mL/min/1.73 m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (eGFR: >80 mL/min/1.73 m^2); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal impairment as compared to that in other renal groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see Dosage and Administration).

Similar recommendations apply to posaconazole modified release tablets; however, a specific study has not been conducted with modified release tablets.

Hepatic impairment

In a small number of subjects (n=12) studied with hepatic impairment (Child-Pugh class A, B or C) receiving posaconazole oral suspension, C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/mL for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/mL) for the normal subjects were consistent with previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26.6, 35.3, and 46.1 hours for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22.1 hours). Due to the limited pharmacokinetic data in patients with hepatic impairment; no recommendation for dose adjustment can be made.

Similar recommendations apply to posaconazole modified release tablets; however, a specific study has not been conducted with the posaconazole modified release tablets.

Electrocardiogram evaluation:

Multiple, time-matched ECGs collected over a 12 hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 85 years of age) administered posaconazole oral suspension 400 mg BD with a high-fat meal. In this pooled analysis, the mean QT_c (Fridericia) interval change was -5 msec following administration of the recommended clinical dose. A decrease in the QT_c (F) interval (- 3 msec) was also observed in a small number of subjects (n=16) administered placebo. No subject administered posaconazole oral suspension had a

QT_c (F) interval of ≥ 500 msec or an increase ≥ 60 msec in their QT_c (F) interval from baseline.

CLINICAL TRIALS

Summary of Posaconazole Oral Suspension studies

Invasive Aspergillosis

Efficacy in patients with refractory disease or intolerance to prior therapy: The efficacy and survival benefit of oral posaconazole for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations), itraconazole or, in a small number of cases, voriconazole or echinocandins, and/or with intolerance to amphotericin B (including liposomal formulations) or itraconazole was demonstrated in 107 patients enrolled in a salvage therapy trial. Patients were administered posaconazole 800 mg/day in divided doses for up to 585 days. The median duration of posaconazole therapy was 56 days (1 – 585 days).

The majority of patients were severely immunocompromised with underlying conditions such as haematological malignancies, including bone marrow transplantation; solid organ transplantation; solid tumours and/or AIDS. An independent expert panel reviewed all patient data, including diagnosis of invasive aspergillosis, refractoriness and intolerance to previous therapy, and clinical outcome in a parallel and blinded fashion with an external control group of 86 patients treated with standard salvage therapy (e.g. amphotericin B including liposomal formulations, and/or itraconazole) mostly at the same time and at the same sites as the patients enrolled in the posaconazole trial.

A success was defined as either complete resolution (complete response) or a clinically meaningful improvement (partial response) of all signs, symptoms and radiographic findings attributable to the fungal infection. Stable, non-progressive disease and failure were considered to be a non-success. Most of the cases of aspergillosis were considered to be refractory in both the posaconazole group (88 %) and in the external control group (79 %) while the remaining patients were intolerant to prior antifungal therapy (12 %, posaconazole; 21 % external control group).

As shown in Table 5, a successful global response at end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group (P=0.006).

Table 5: Overall efficacy of posaconazole oral suspension at the end of treatment* for invasive aspergillosis in comparison to an external control group

	Posaconazole	External Control Group
Overall Response	45/107 (42 %)	22/86 (26 %)
	Adjusted Odds Ratio ** 4.06 (95 % CI: 1.50, 11.04) P=0.006	
	Unadjusted Odds ratio 2.11 (95 % CI: 1.14, 3.92) P=0.018	
Survival at day 365	**(38 %)**	**(22 %)**
Success by Species		
All mycologically confirmed *Aspergillus* spp.***	34/76 (45 %)	19/74 (26 %)
A. fumigatus	12/29 (41 %)	12/34 (35 %)
A. flavus	10/19 (53 %)	3/16 (19 %)
A. terreus	4/14 (29 %)	2/13 (15%)
A. niger	3/5 (60 %)	2/7 (29%)

* end of all study drug therapy plus 7 days within 372 days of the start of salvage therapy

** adjusted odds ratio was obtained using a logistic regression model adjusting for major covariates

*** includes other less common species or species unknown

Other Serious Fungal Pathogens

Posaconazole has been shown to be effective against the following additional pathogens when other therapy had been ineffective or when the patient had developed intolerance of the prior therapy:

Zygomycosis: Successful responses to posaconazole therapy were noted in 7/13 (54 %) of patients with zygomycete infections. Sites of infection included the sinuses, lung, and skin. Organisms included Rhizopus, Mucor and Rhizomucor. Most of the patients had underlying haematological malignancies, half of which required a bone marrow transplant. Half of the patients were enrolled with intolerance to previous therapy and the other half as a result of disease that was refractory to prior therapy. Three patients were noted to have disseminated disease, one of which had a successful outcome after failing amphotericin B therapy.

Fusarium spp.: Successful responses to posaconazole therapy were seen in 11 of 24 (46 %) of patients with fusariosis. Four of the responders had disseminated disease and one patient had disease localized to the eye; the remainder had a variety of sites of infection. Seven of 24 patients had profound neutropenia at baseline. In addition, 3/5 patients with infection due to *F. solani* which is typically resistant to most antifungal agents, were successfully treated.

Chromoblastomycosis/Mycetoma: Successful responses to posaconazole therapy were seen in 9 of 11 (82 %) of patients with chromoblastomycosis or mycetoma. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis: The efficacy of posaconazole in the primary treatment of non-meningeal coccidioidomycosis was demonstrated in 15 clinically evaluable patients enrolled in an open-label, non-comparative trial to receive posaconazole 400 mg daily for 6 months. Most patients were otherwise healthy and had infections at a

variety of sites. A satisfactory response (defined as an improvement of at least 50 % of the Cocci score as defined by the BAMSG Coccidioidomycosis trial group) was seen in 12 of 15 patients (80 %) after an average of 4 months of posaconazole treatment. In a separate open-label, non-comparative trial, the safety and efficacy of posaconazole 400 mg twice a day was assessed in 16 patients with coccidioidomycosis infection refractory to standard treatment.

Most had been treated with amphotericin B (including lipid formulations) and/or itraconazole or fluconazole for months to years prior to posaconazole treatment. At the end of treatment with posaconazole, a satisfactory response (complete or partial resolution of signs and symptoms present at baseline) as determined by an independent panel was achieved for 11/16 (69 %) of patients. One patient with CNS disease that had failed fluconazole therapy had a successful outcome following 12 months of posaconazole therapy.

Treatment of Azole-Susceptible Oropharyngeal Candidiasis (OPC) in HIV-infected patients

A randomised, double-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis. The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical and mycological response rates from the above study are shown in Table 6 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole demonstrated a significantly better mycological response rate than fluconazole 4 weeks after the end of treatment.

Table 6: Clinical Success Rates and Mycological Response Rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical Success Rate at Day 14	91.7 % (155/169)	92.5 % (148/160)
Clinical Success Rate 4 Weeks After End of Treatment	68.5 % (98/143)	61.8 % (84/136)
Mycological Response Rate 4 Weeks After End of Treatment*	40.6 % (41/101)	26.4 % (24/91)

*Statistically significant (P=0.0376)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

Mycological response rate was defined as mycological success (≤ 20 CFU/mL) divided by the total number of cases eligible for analysis.

Treatment of Oropharyngeal Candidiasis refractory to Itraconazole and Fluconazole (rOPC) in HIV-infected patients

The primary efficacy parameter in the short-term treatment study was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole 400 mg twice a day with an option for further treatment during a 3-month maintenance period. A 75 % (132/176) clinical success rate and a 36.5 % (46/126) mycological response rate (≤ 20 CFU/ml) were achieved

after 4 weeks of posaconazole treatment. Clinical success rates ranged from 71 % to 100 %, inclusive, for all azole-resistant *Candida* species identified at Baseline, including *C. glabrata* and *C. krusei*.

In the long-term treatment study the primary efficacy endpoint was the clinical success rate (cure or improvement) after 3 months of treatment. A total of 100 HIV-infected patients with OPC and/or EC were treated with posaconazole 400 mg twice a day for up to 15 months. Sixty of these patients had been previously treated in Study 330. An 85.6 % (77/90) clinical success rate overall (cure or improvement) was achieved after 3 months of posaconazole treatment; 80.6 % (25/31) for previously untreated subjects.

The mean exposure to posaconazole based on the actual days dosed was 102 days (range: 1-544 days). Sixty-seven percent (67 %, 10/15) of patients treated with posaconazole for at least 12 months had continued clinical success at the last assessment.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899):

Two large, randomised, controlled studies were conducted using posaconazole as prophylaxis for the prevention of IFIs among patients at high risk.

Study 316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic HSCT recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomisation as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medication + 7 days). The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole).

Study 1899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomisation. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole).

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. There were significantly fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole or itraconazole. See Table 7 for results from both studies.

Table 7: Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections

Study 316: Allogeneic Hematopoietic Stem Cell Transplant Recipients with Graft vs. Host Disease			
	Posaconazole n =301	**Fluconazole n = 299**	**P-Value**
On therapy plus 7 days			
Clinical Failure	50 (17%)	55 (18%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	22 (7%)	0.0038
(Aspergillus)	3 (1%)	17 (6%)	0.0059
(*Candida*)	1 (<1%)	3 (1%)	
(Other)	3 (1%)	2 (1%)	
Through 16 weeks			
Clinical Failure	99 (33%)	110 (37%)	
Failure due to:			
Proven/Probable IFI	16 (5%)	27 (9%)	0.0740
(Aspergillus)	7 (2%)	21 (7%)	0.0013
(*Candida*)	4 (1%)	4 (1%)	
(Other)	5 (2%)	2 (1%)	
Study 1899: Neutropenic Patients with Acute Myelogenous Leukaemia/Myelodysplastic Syndromes			
	Posaconazole n =304	**Fluconazole/Itraconazole n = 298**	**P-Value**
On therapy plus 7 days			
Clinical Failure	82 (27%)	126 (42%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	25 (8%)	0.0009
(Aspergillus)	2 (1%)	20 (7%)	0.0001
(*Candida*)	3 (1%)	2 (1%)	
(Other)	2 (1%)	3 (1%)	
Through 100 days post-randomisation			
Clinical Failure	158 (52%)	191 (64%)	
Failure due to:			
Proven/Probable IFI	14 (5%)	33 (11%)	0.0031
(Aspergillus)	2 (1%)	26 (9%)	<0.0001
(*Candida*)	10 (3%)	4 (1%)	
(Other)	2 (1%)	3 (1%)	

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomisation, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) (Figure 1) as well as IFI-related deaths (P = 0.0209).

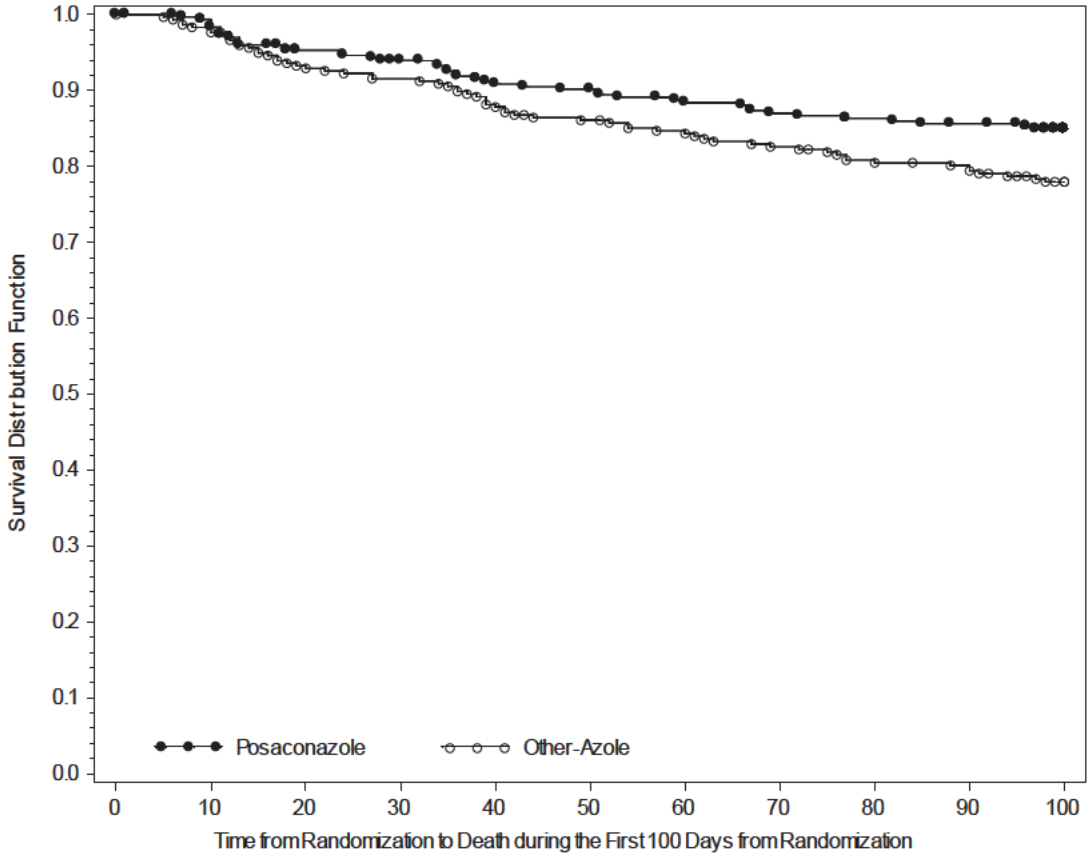


Figure 1: All cause mortality in Study 1899 (POS vs FLU/ITZ; P= 0.0354)

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Use in paediatric patients:

A total of 16 patients aged 8 to 17 years were included in the posaconazole oral suspension therapeutic trials of invasive fungal infections. Five patients were < 13 years of age and 11 were 13 -17 years old. Infections included aspergillosis, candidiasis and fusariosis. Successful response after treatment with posaconazole at divided doses up to 800 mg/day was seen in 50 % (8/16) of patients. Pharmacokinetic parameters obtained from 12 of these patients were not different from those obtained from the patients in the 18-65 year age group, and the safety profile appeared similar.

Additionally, 12 patients aged 13 to 17 years received 600 mg/day of posaconazole oral suspension for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears to be similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

Safety and efficacy in paediatric patients below the age of 13 years have not been established.

Summary of Posaconazole Modified Release Tablet studies

Study 5615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole modified release

tablet. Study 5615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program. The pharmacokinetics and safety data from Study 5615 were bridged to the existing data (including efficacy data) with the oral suspension.

Study 5615 enrolled a total of 230 subjects. Part 1 of the study was designed to select a dose for further study in Part 2, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Part 2 of the study was designed to evaluate posaconazole modified release tablet in a more diverse patient population, and to confirm the exposure of posaconazole modified release tablet in additional subjects at risk of a fungal infection. Posaconazole modified release tablet was administered without regard to food intake in both Part 1 and Part 2 of the study.

The subject population for Part 1 included subjects with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Part 1: 200 mg BD on Day 1, followed by 200 mg QD thereafter (Part 1A) and 300 mg BD on Day 1, followed by 300 mg QD thereafter (Part 1B).

The subject population in Part 2 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Part 1, all subjects in Part 2 received 300 mg BD on Day 1, followed by 300 mg QD thereafter.

The total subject population had a mean age of 51 years (range = 19-78 years), 93% were White, the major ethnicity was not Hispanic or Latino (84%), and 62% were male. The study treated 110 (48%) subjects with AML (new diagnosis), 20 (9%) subjects with AML (first relapse), 9 (4%) subjects with MDS, and 91 (40%) subjects with HSCT, as the primary diseases at study entry.

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. This serial PK analysis demonstrated that 90% of the subjects treated with the 300 mg QD dose attained steady state C_{avg} between 500-2500 ng/mL. [C_{avg} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).] Subjects with AML/MDS with neutropenia following chemotherapy or HSCT subjects receiving immunosuppressive therapy to prevent or treat GVHD who received 300 mg QD achieved a mean C_{avg} at steady state of 1580 ng/mL. The PK findings from the pivotal study (Study 5615) support a 300-mg daily dose of posaconazole modified release tablet for use in prophylaxis.

INDICATIONS

NOXAFIL (posaconazole) is indicated for use in the treatment of the following invasive fungal infections in patients 13 years of age or older:

- Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy.
- Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.

NOXAFIL is also indicated for the:

- Treatment of oropharyngeal candidiasis in immunocompromised adults, including patients with disease that is refractory to itraconazole and fluconazole.
- Prophylaxis of invasive fungal infections among patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

For patients being treated for oropharyngeal candidiasis, only the oral suspension should be used.

CONTRAINDICATIONS

NOXAFIL is contraindicated in patients with known hypersensitivity to posaconazole or to any of the excipients.

Coadministration of posaconazole and ergot alkaloids (ergotamine, dihydroergotamine) is contraindicated as posaconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism (See Interactions with other medicines).

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolised through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

Although not studied *in vitro* or *in vivo,* coadministration of posaconazole and certain drugs metabolised through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozide, and quinidine may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (See Interactions with other medicines).

PRECAUTIONS

Hypersensitivity:

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles. Subjects with severe or serious reactions to azoles were excluded from key studies of posaconazole.

Hepatic toxicity:

In clinical trials, there were infrequent cases of hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis) during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalized without interruption of therapy and rarely required drug discontinuation. Rarely, more severe hepatic reactions (including cases that have progressed to fatal outcomes) were reported in patients with serious underlying medical conditions (e.g. haematological malignancy) during treatment with posaconazole. In the clinical pharmacology program, no healthy subject had CTC Grade 3 or Grade 4 (>5 x ULN) elevations in their liver function test results. Most of these LFT changes were mild in severity and all were transient in nature, returned to baseline after the cessation of dosing, and rarely led to study discontinuation. See Table 8 for hepatic enzyme abnormalities in healthy volunteers.

Table 8: Summary of Hepatic Enzyme Abnormalities in the Healthy Volunteers

CTC Grade	AST		ALT		GGT	
	POS n=444	Placebo n=48	POS n=444	Placebo n=48	POS n=431	Placebo n=47
0 (≤1 x ULN)	417 (94%)	48 (100%)	388 (87%)	46 (96%)	408 (95%)	46 (98%)
1 (>1 - 2.5 x ULN)	26 (6%)	0 (0%)	50 (11%)	1 (2%)	20 (5%)	1 (2%)
2 (>2.5 - 5 x ULN)	1 (<1%)	0 (0%)	6 (1%)	1 (2%)	3 (1%)	0 (0%)

CTC=Common Toxicity Criteria; ULN=upper limit of normal

Note: The majority of subjects had CTC Grade 0 liver function test (LFTs) at baseline. This table summarizes the worst CTC grade observed during the treatment phase per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included in the summary.

QT prolongation:

Some azoles have been associated with prolongation of the QT_c interval on the electrocardiogram (ECG). Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with medicines that are known to prolong the QTc interval and are metabolised through the CYP3A4 (See Pharmacokinetic Properties – Electrocardiogram evaluation, Contraindications, Interactions with other medicines).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Vincristine toxicity:

Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative treatment options (see Interactions with other medicines).

Effects on Fertility:

Posaconazole had no effect on the fertility of male rats at doses up to 180 mg/kg/day (1.6 times the maximum recommended clinical dose (RCD) based on AUC at steady state in healthy volunteers fed a high fat meal). Like other azoles, male dogs administered oral posaconazole had findings consistent with reduced plasma testosterone levels, including spermatic giant cells (relative exposure 4.2). Posaconazole administered to female rats at doses up to 45 mg/kg/day (relative exposure 2.0) for 2 weeks prior to mating did not affect fertility, but disruption of oestrus cycling was seen in female rats treated for 4 weeks.

Use in Pregnancy:

Pregnancy Category B3 – There are no adequate studies in pregnant women. A total of three pregnancies have been reported in female subjects treated with posaconazole oral suspension. Two pregnancies were electively terminated; no examination was reported on the foetuses. Another pregnancy was diagnosed at a follow-up visit approximately 1 month after the completion of a full 16-week prophylactic treatment with POS oral suspension 200 mg TDS in a patient who had received an allogeneic haematopoietic stem cell transplant. The subject delivered a healthy full-term male infant via caesarean section.

Studies in rats have shown reproductive toxicity including post implantation loss, increased skeletal variations, teratogenicity (craniofacial malformations), increased gestation length, dystocia, and reduced postnatal viability at exposure levels lower than those expected at the recommended doses in humans. An increase in post implantation loss and increased skeletal variations were seen in rabbits at plasma exposure levels greater than those of humans receiving therapeutic doses of posaconazole.

NOXAFIL must not be used during pregnancy unless the benefit to the mother clearly outweighs the risk to the foetus. Women of childbearing potential must be advised to always use effective contraceptive measure during treatment and for at least 2 weeks after completing therapy.

Use in Lactation:

Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Women taking posaconazole should not breastfeed.

Paediatric Use:

(See Clinical Pharmacology – Pharmacokinetics in special populations, Paediatric). Safety and effectiveness in paediatric patients below the age of 13 years have not been established. Clinical experience of posaconazole oral suspension in paediatric patients 13 - 17 years of age is very limited (n=16), therefore pharmacology, efficacy and safety profiles have not been completely characterised in children within this age group. Available data suggest a similar profile in children 13 - 17 years of age and adults.

Use of posaconazole modified release tablets in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension.

Use in the Elderly:

No dosage adjustment is recommended for geriatric patients (See Clinical Pharmacology – Pharmacokinetics in special populations – Elderly).

Of the 230 patients treated with posaconazole modified release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole modified release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Effects on Adrenal Steroid Hormones:

As observed with other azole antifungal agents, effects related to inhibition of adrenal steroid hormone synthesis were seen in repeat-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Carcinogenicity:

Posaconazole caused an increase in hepatocellular adenomas in mice at plasma exposure levels ~7-times higher than anticipated in humans at the maximum recommended clinical dose. This finding is considered to have occurred secondary to liver toxicity in the species, and mice are known to be particularly susceptible to this neoplastic change.

Rats treated with posaconazole at exposure levels ≥ 2.4-times that of humans developed adrenal cortical cell adenomas and/or carcinomas and phaeochromocytomas. The cortical tumours are consistent with endocrinological disruption following chronic impairment of adrenal steroidogenesis. The increase in phaeochromocytomas is considered to be a rat-specific phenomenon that follows changes in calcium homeostasis. Altered calcium homeostasis has not been observed in humans receiving posaconazole oral suspension. The results of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

Genotoxicity:

Posaconazole has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, mammalian mutation and human lymphocyte chromosomal aberration) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, posaconazole did not cause genetic damage.

Interactions with other medicines:

Table 9: Summary of Drug Interactions

Contraindicated	Avoid concomitant use unless the benefit outweighs the risk	Dose adjustment of other medications and/or monitoring of adverse events	No dose adjustment required
Ergotamine or dihydroergotamine	Rifabutin	Rifabutin	Antacids
Terfenadine, astemizole	Phenytoin	Cyclosporine	Zidovudine, ritonavir, lamivudine, indinavir
Cisapride	Cimetidine	Tacrolimus	Glipizide
Pimozide	Efavirenz	Sirolimus	
Quinidine	Vinca alkaloids		
Halofantrine		Midazolam	
HMG-CoA reductase inhibitors primarily metabolised through CYP3A4		Atazanavir/ritonavir Fosamprenavir	
		Calcium channel blockers metabolised through CYP3A4	
		Sulfonylureas	
		Digoxin	

Note that the majority of the interaction studies were carried out in healthy volunteers with repeat dose regimens of posaconazole 400 mg (oral suspension) twice daily administered with a meal or nutritional supplement. See below for further information.

Effect of Other Drugs on Posaconazole

Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations.

Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole by 43 % and 49 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk.

Cimetidine (400 mg twice a day) decreased the C_{max} and AUC of posaconazole oral suspension 200 mg once a day each by 39 %. Concomitant use of posaconazole and cimetidine should be avoided unless the benefit outweighs the risk. The effect of other H_2 receptor antagonists and proton pump inhibitors that may suppress gastric acidity has not been studied. Reduction in bioavailability may occur, therefore co-administration of posaconazole with H_2 receptor antagonists and proton pump inhibitors should be avoided if possible.

Antacids

Posaconazole oral suspension: 20 mL single dose of liquid antacid, equivalent to 25.4 mEq acid neutralizing capacity/5mL, had no clinically significant effect on posaconazole oral suspension C_{max} and AUC. No dosage adjustments are required.

Posaconazole modified release tablet: No clinically relevant effects were observed when posaconazole modified release tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors. No dosage adjustment of posaconazole modified release tablets is required when posaconazole modified release tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors.

Glipizide: (10 mg single dose) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Ritonavir (600 mg twice a day) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Efavirenz: (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45% and 50%, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. A study conducted in 20 healthy volunteers, repeat dose administration of fosamprenavir (700 mg twice a day for 10 days) decreased the C_{max} and AUC of posaconazole (200 mg once a day on the 1st day, 200 mg twice a day on the 2nd day, then 400 mg twice a day for 8 Days) by 21 % and 23 %, respectively. The GMRs of posaconazole C_{max} and AUC when taken as posaconazole versus posaconazole/fosamprenavir were 0.79 (0.71–0.89) and 0.77 (0.68–0.87), respectively.

Effects of Posaconazole on Other Drugs

Posaconazole is not metabolised to a clinically significant extent through the cytochrome P450 system. However, posaconazole is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolised through this enzyme pathway may increase when administered with posaconazole.

Terfenadine, astemizole, cisapride, pimozide, and quinidine: Although not studied *in vitro* or *in vivo,* co-administration of posaconazole and certain drugs such as terfenadine, astemizole, cisapride, pimozide, and quinidine, metabolised through the CYP3A4 system may result in increased plasma concentrations of these drugs, leading to potentially serious and/or life threatening adverse events (QT prolongation and rare occurrences of torsade de pointes). Therefore, co-administration of these drugs with posaconazole is contraindicated (See Contraindications).

Ergot alkaloids: Although not studied *in vitro* or *in vivo*, posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Coadministration of posaconazole and ergot alkaloids is contraindicated (See Contraindications).

Vinca alkaloids: Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see Precautions). Posaconazole may increase plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Cyclosporine: In heart transplant patients on stable doses of cyclosporine, posaconazole 200 mg once daily increased cyclosporine concentrations requiring dose reductions. Cases of elevated cyclosporine levels resulting in serious adverse events, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving cyclosporine, the dose of cyclosporine should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of cyclosporine should be adjusted as necessary.

Tacrolimus: Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9 fold, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during coadministration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

Rifabutin: Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If the drugs are coadministered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam: Repeat dose administration of oral posaconazole 200 mg or 400 mg twice daily with a high fat meal, significantly increased the midazolam C_{max} by 2.2 fold (~7.03 to 15.4 ng/mL): AUC by approximately 5 fold (~31.9 to 159 h.ng/mL); and prolonged the mean terminal half-life of midazolam 8 to 10 hours in healthy subjects. It is recommended that dose adjustments of benzodiazepines, including midazolam metabolised by CYP3A4, be considered during co-administration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), ritonavir, indinavir: In HIV infected patients on stable doses of zidovudine (300 mg twice a day or 200 mg every 8 hours), lamivudine (150 mg twice a day), ritonavir (600 mg twice a day) and/or indinavir (800 mg every 8 hours), posaconazole had no clinically significant effect on the C_{max} and AUC of these medicinal products. Although not considered clinically significant, ritonavir exposure was increased by 30% with the addition of posaconazole.

HMG-CoA reductase inhibitors primarily metabolised through CYP3A4: Repeat dose administration of oral posaconazole (50, 100, and 200 mg once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased statins concentrations in plasma can be associated with rhabdomyolysis. Co-administration of posaconazole and HMG-CoA reductase inhibitors primarily metabolised through CYP3A4 is contraindicated.

Interactions with HMG CoA reductase inhibitors that are not metabolised by CYP3A4 have not been investigated but clinically relevant drug interactions are not expected as posaconazole does not inhibit other CYP isoenzymes at relevant concentrations.

Calcium channel blockers metabolised through CYP3A4: Although not studied *in vitro* or *in vivo*, frequent monitoring for adverse effects and toxicity related to calcium channel blockers is recommended during coadministration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin: Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas: Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

HIV Protease Inhibitors: As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir (300 mg once a day for 7 days) an average of 2.6-fold and 3.7-fold, respectively, in healthy subjects. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir to a lesser extent when administered as a boosted regimen with ritonavir (300 mg atazanavir plus ritonavir 100 mg once a day for 7 days) with an average of 1.5-fold and 2.5-fold, respectively, in healthy subjects. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Fosamprenavir: The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown. A study conducted in 20 healthy subjects, administration of posaconazole (200 mg once a day on the 1st day, 200 mg twice a day on the 2nd day, then 400 mg twice a day for 8 Days) with fosamprenavir (700 mg twice a day for 10 days) resulted in a 36 % and 65 % lower C_{max} and AUC for amprenavir compared to when fosamprenavir was administered with ritonavir. The GMRs of amprenavir C_{max} and AUC when taken as fosamprenavir and

posaconazole versus fosamprenavir/ritonavir were 0.64 (0.55–0.76) and 0.35 (0.32–0.39), respectively.

ADVERSE EFFECTS

Posaconazole Oral Suspension

Drug-related adverse reactions observed in 2 400 subjects dosed with posaconazole oral suspension are shown in Table 10. 172 patients received posaconazole oral suspension therapy for ≥ 6 months; 58 of these received posaconazole oral suspension therapy for ≥ 12 months.

The most frequently reported adverse reactions reported across the whole population of healthy volunteers and patients were nausea (6 %) and headache (6 %).

Table 10: Treatment-related adverse reactions reported in posaconazole oral suspension dosed subjects by body system and frequency N=2400

Common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000)

Infections and infestations	
Uncommon:	oral candidiasis, sinusitis
Rare:	catheter related infection, non herpetic cold sores, oesophageal candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	anaemia, thrombocytopenia, leukopenia, eosinophilia, lymphadenopathy
Rare:	abnormal blood gases, haemolytic uraemic syndrome, neutrophilia, pancytopenia, coagulation disorder, haemorrhage NOS, platelet count increased, prothrombin decreased, prothrombin time prolonged, purpura, thrombotic thrombocytopenic purpura
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction, Stevens Johnson syndrome
Endocrine disorders	
Rare:	adrenal insufficiency, gonadotropins decreased
Metabolism and nutrition disorders	
Common:	anorexia, electrolyte imbalance
Uncommon:	hyperglycaemia, hypertriglyceridaemia, hyperuricaemia, weight decrease, LDH increased, dehydration
Rare:	amylase increased, hypercholesterolemia, hyperlipaemia, hyperproteinaemia, hypoalbuminaemia, lipase increased, metabolic acidosis, renal tubular acidosis, vitamin K deficiency, weight increase

Psychiatric disorders	
Uncommon:	altered mental status, anxiety, confusion, insomnia
Rare:	amnesia, depression, abnormal dreaming, emotional lability, libido decreased, paroniria, psychosis
Nervous system disorders	
Common:	dizziness, headache, paresthesia, somnolence
Uncommon:	neuropathy, hypoesthesia, convulsions, tremor
Rare:	peripheral neuropathy, areflexia, ataxia, cognition impaired, delirium, dysphonia, dystonia, encephalopathy, hemiparesis, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, impaired concentration, memory impairment, meningism, mononeuritis, restless leg syndrome, sciatica, syncope
Eye disorders	
Uncommon:	conjunctivitis, blurred vision
Rare:	eye pain, eyes dry, periorbital oedema, diplopia, photophobia, scotoma
Ear and labyrinth disorder	
Uncommon:	earache, vertigo
Rare:	hearing impairment, tinnitus
Cardiac disorders	
Uncommon:	abnormal ECG, QTc/QT prolongation, atrial flutter, atrial fibrillation, bundle branch block, tachycardia, extrasystoles, palpitation, ventricular hypertrophy
Rare:	bradycardia, cardiac failure, cardio-respiratory arrest, sudden death, ventricular tachycardia, aortic valve sclerosis, cardiomegaly, ejection fraction decreased, mitral valve disease NOS, myocardial infarction, supraventricular tachycardia, premature atrial contractions, premature ventricular contractions, AV block, torsades de pointes
Vascular disorders	
Uncommon:	flushing, hot flushes, hypertension, hypotension
Rare:	atherosclerosis, cerebrovascular accident, deep venous thrombosis NOS, pulmonary embolism, ischemia, haematoma
Respiratory, thoracic and mediastinal disorders	
Uncommon:	chest pain, coughing, dyspnoea, epistaxis, pharyngitis, nasal congestion
Rare:	atelectasis, dry throat, pulmonary hypertension, interstitial pneumonia, nasa irritation, pneumonitis, postnasal drip, pulmonary infiltration, rales, rhinitis, rhinorrhoea
Gastrointestinal disorders	

Common:	abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Uncommon:	taste perversion, constipation, loose stools, abdominal distention, dysphagia, ascites, eructation, thirst, gastritis, gastroesophageal reflux, mucositis NOS, oesophagitis, pancreatitis, tongue discolouration
Rare:	gastrointestinal tract haemorrhage, ileus, abdominal tenderness, cheilitis, haemorrhagic diarrhoea, oesophagus ulceration, haemorrhagic gastritis, odynophagia, pancreatic enzymes NOS increased, proctalgia, retching, aphthous stomatitis, tenesmus, melena, gingivitis, glossitis
Hepatobiliary disorders	
Common:	elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
Uncommon:	hepatitis, hepatocellular damage, hepatomegaly, jaundice
Rare:	asterixis, cholestasis, hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, splenomegaly
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	alopecia, dry skin, maculopapular rash, urticaria, furunculosis, acne, mouth ulceration, pruritus, pruritic rash
Rare:	stomatitis, dermatitis, erythema, erythematous rash, follicular rash, macular rash, night sweats, seborrhoea, skin nodule, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	myalgia, arthralgia, back pain, musculoskeletal pain, flank pain, muscle weakness
Rare:	bone pain, chest wall pain, fasciitis, neck stiffness, cramps extremities, muscle cramps
Renal and urinary disorders	
Uncommon:	albuminuria, altered micturition frequency, dysuria, increased blood creatinine, acute renal failure, renal failure, haematuria, renal impairment, nocturia
Rare:	increased BUN, interstitial nephritis, micturition disorder, renal calculus, urinary tract obstruction NOS
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	leukorrhoea, breast pain
General disorders and administration site conditions	
Common:	asthenia, fatigue, fever

Uncommon:	increased sweating, pain, rigors, malaise, weakness, oedema, tooth discolouration
Rare:	face oedema, tongue oedema
Investigations	
Uncommon:	altered drug levels
Injury, poisoning and procedural complications	
Uncommon:	drug toxicity (NOS)
Rare:	ecchymoses

Serious adverse events that were considered treatment related were reported in 8 % (35/428) of patients in the refractory invasive fungal infection pool. Most individual treatment related serious adverse events were reported by <1 % of patients and are largely reflective of the serious underlying conditions that predisposed to the development of the invasive fungal infection. Treatment related serious adverse events reported in 1 % of subjects (3 or 4 subjects each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting. Treatment-related serious adverse events reported in 605 patients treated with posaconazole oral suspension for prophylaxis (1 % each) included bilirubinaemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with posaconazole oral suspension have included adrenal insufficiency, pancreatitis, allergic and/or hypersensitivity reactions.

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. A pooled analysis of 173 posaconazole oral suspension-dosed healthy volunteers utilizing time matched ECGs did not show a potential to prolong the QT interval. In addition, rare cases of torsade de pointes have been reported in patients taking posaconazole oral suspension

In addition, rare cases of haemolytic uremic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

Table 11: Treatment-related adverse events reported in ≥ 1 % of patients treated for invasive fungal infections with posaconazole oral suspension (Severity as classified by the investigator)

Disorder	Total (All) n=330 Number (%)	Total (Mild/Moderate) n=330 Number (%)	Total (Severe/Life-Threatening) n=330 Number (%)
Body as a Whole-General			
anorexia	8 (2)	8 (2)	0
asthenia	4 (1)	4 (1)	0
chest pain	2 (1)	2 (1)	0
dizziness	7 (2)	6 (2)	1 (<1)
drug level altered	7 (2)	4 (1)	3 (1)
fatigue	7 (2)	6 (2)	1 (<1)
fever	3 (1)	3 (1)	0
headache	15 (5)	13 (4)	2 (1)
weakness	2 (1)	2 (1)	0
Cardiovascular, general			
cardio-respiratory arrest	2 (1)	0	2 (1)
ventricular hypertrophy	2 (1)	1 (<1)	1 (<1)
Central and Peripheral Nervous System			
confusion	3 (1)	3 (1)	0
convulsions	2 (1)	0	2 (1)
hyperreflexia	2 (1)	2 (1)	0
hypoesthesia	2 (1)	2 (1)	0
mental status, altered	2 (1)	2 (1)	0
paresthesia	6 (2)	6 (2)	0
somnolence	3 (1)	3 (1)	0
tremor	2 (1)	2 (1)	0
Blood and lymphatic system	6 (2)	4 (1)	2 (1)
anaemia	4 (1)	3 (1)	1 (<1)
Eye	4 (1)	3 (1)	1 (<1)

Disorder	Total (All) n=330 Number (%)	Total (Mild/Moderate) n=330 Number (%)	Total (Severe/Life-Threatening) n=330 Number (%)
vision blurred	2 (1)	2 (1)	0
Reproductive system and breast			
breast pain	1 (<1)	1 (<1)	0
menstrual disorder (based on females only)	2 (2)	2 (2)	0
Gastro-intestinal system			
abdominal distension	2 (1)	2 (1)	0
abdominal pain	16 (5)	13 (4)	3 (1)
constipation	2 (1)	2 (1)	0
diarrhoea	11 (3)	10 (3)	1 (<1)
dyspepsia	2 (1)	2 (1)	0
flatulence	3 (1)	3 (1)	0
mouth dry	5 (2)	5 (2)	0
nausea	31 (9)	2 (1)	29 (9)
vomiting	19 (6)	18 (5)	1 (<1)
Heart Rate and Rhythm			
atrial flutter	2 (1)	1 (<1)	1 (<1)
ECG abnormal specific	2 (1)	2 (1)	0
extrasystoles	2 (1)	1 (<1)	1 (<1)
fibrillation atrial	3 (1)	2 (1)	1 (<1)
QTc/QT prolongation	6 (2)	6 (2)	0
tachycardia	2 (1)	2 (1)	0
tachycardia supraventricular	2 (1)	1 (<1)	1 (<1)
Injury and poisoning			
drug toxicity (NOS)	2 (1)	0	2 (1)
Liver and biliary system			
bilirubinemia	4 (1)	3 (1)	1 (<1)
gamma-GT increased	2 (1)	0	2 (2)

Disorder	Total (All) n=330 Number (%)	Total (Mild/Moderate) n=330 Number (%)	Total (Severe/Life-Threatening) n=330 Number (%)
hepatic enzymes increased	7 (2)	6 (2)	1 (<1)
hepatic function abnormal	2 (1)	2 (1)	0
jaundice	2 (1)	1 (<1)	1 (<1)
AST increased	9 (3)	6 (2)	3 (1)
ALT increased	11 (3)	9 (3)	2 (1)
Metabolic and nutritional			
phosphatase alkaline increased	6 (2)	5 (2)	1 (<1)
thirst	2 (1)	2 (1)	0
Musculo-skeletal system			
musculo-skeletal pain	2 (1)	2 (1)	0
Platelet, bleeding and clotting			
thrombocytopenia	2 (1)	2 (1)	0
Renal & Urinary System			
blood creatinine decreased	5 (2)	4 (2)	1 (<1)
nocturia	2 (1)	2 (1)	0
renal failure	2 (1)	1 (<1)	1 (<1)
renal failure acute	2 (1)	0	2 (1)
Skin/ subcutaneous tissue			
alopecia	4 (1)	4 (1)	0
dry skin	3 (1)	3 (1)	0
pruritus	3 (1)	3 (1)	0
rash	9 (3)	7 (2)	2 (1)
rash maculopapular	4 (1)	3 (1)	1 (<1)
rash vesicular	2 (1)	2 (1)	0

Table 12: Treatment-related, treatment-emergent adverse events (any grade): ≥ 2 % of subjects (OPC) with posaconazole oral suspension

Adverse event	**Number (%) of subjects**		
	Controlled OPC pool		**Refractory OPC pool**
	POS n = 557	**FLU n = 262**	**POS n = 239**
Subjects reporting any adverse event[a]	150 (27)	70 (27)	135 (56)
Body as a whole – general disorders			
Anorexia	6 (1)	1 (< 1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Headache	16 (3)	5 (2)	18 (8)
Central and peripheral nervous system disorders			
Somnolence	4(1)	5 (2)	3 (1)
Disorders of blood and lymphatic system			
Anaemia	2 (< 1)	0 (0)	6 (3)
Neutropenia	10 (2)	4 (2)	20 (8)
Gastro-intestinal system disorders			
Abdominal pain	10 (2)	8 (3)	12 (5)
Diarrhoea	19 (3)	13 (5)	26 (11)
Flatulence	6 (1)	0 (0)	11 (5)
Mouth dry	7 (1)	6 (2)	5 (2)
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Liver and biliary system disorders			
Hepatic enzymes increased	1 (< 1)	0 (0)	5 (2)
Hepatic function abnormal	3 (1)	4 (2)	0 (0)
Metabolic and nutritional disorders			
Phosphatase alkaline increased	3 (1)	3 (1)	5 (2)
Musculo-skeletal system disorders			
Myalgia	1 (<1)	0 (0)	4 (2)
Platelet, bleeding and clotting disorders			
Thrombocytopenia	3 (1)	0 (0)	4 (2)

Adverse event	Number (%) of subjects		
	Controlled OPC pool		Refractory OPC pool
	POS n = 557	FLU n = 262	POS n = 239
Psychiatric disorders			
Insomnia	3 (1)	0 (0)	6 (3)
Skin and subcutaneous tissue disorders			
Pruritus	6 (1)	2 (1)	5 (2)
Rash	8 (1)	4 (2)	10 (4)

[a] number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

Table 13: Studies 316 and 1899, Treatment-related, treatment-emergent adverse events: All (≥ 2% incidence) and Severe/Life Threatening Number (%) of Subjects (Prophylaxis) in the Posaconazole oral suspension or Fluconazole treatment groups

	POS n=605		FLU n=539		ITC n=58	
	All	**Severe/LT**	**All**	**Severe/LT**	**All**	**Severe/LT**
Subjects reporting any adverse event[a]	209 (35)	81 (13)	186 (35)	53 (10)	30 (52)	6 (10)
Gastro-Intestinal System Disorders						
Abdominal Pain	13 (2)	1 (< 1)	15 (3)	2 (< 1)	1 (2)	0
Constipation	4 (1)	0	12 (2)	0	0	0
Diarrhoea	28 (5)	4 (1)	24 (4)	1 (<1)	9 (16)	0
Dyspepsia	8 (1)	1 (<1)	9 (2)	0	0	0
Nausea	44 (7)	5 (1)	45 (8)	1 (<1)	8 (14)	0
Vomiting	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
Heart Rate and Rhythm Disorders						
QTc/QT Prolongation	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
Liver and Biliary System Disorders						
Bilirubinemia	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT Increased	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
Hepatic Enzymes Increased	15 (2)	11 (2)	10 (2)	3 (1)	0	0
AST Increased	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
ALT Increased	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	1 (2)
Metabolic and Nutritional Disorders						
Hypokalemia	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders						
Rash	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

GGT = gamma glutamyl transpeptidase; ALT = serum glutamic oxaloacetic transaminase; ALT = serum glutamic pyruvic transaminase

[a] number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

Posaconazole Modified Release Tablets

In clinical trials, the type and frequency of adverse effects reported for posaconazole modified release tablets were generally similar to that reported in trials of posaconazole oral suspension.

The safety of posaconazole modified release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole modified release tablets when given as antifungal prophylaxis (P05615). Patients were immunocompromised with

underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17% of patients were ≥65 years of age), and were 93% white and 16% Hispanic. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following BD dosing on Day 1 in each cohort).

The most frequently reported treatment-related adverse reactions (≥5%) with posaconazole modified release tablets (300 mg once daily) were nausea and diarrhoea. The most frequently reported adverse reaction leading to discontinuation of posaconazole modified release tablets 300 mg once daily was nausea.

Table 14 presents treatment-emergent adverse reactions observed in patients treated with 300 mg daily dose at an incidence of ≥10% in posaconazole modified release tablet study.

Table 14: Posaconazole Study 5615: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System Preferred Term	Posaconazole Tablet (300 mg) (n=210)	
Subjects Reporting any Adverse Reaction	201	(99)
Blood and Lymphatic System Disorder		
Anemia	22	(10)
Febrile Neutropenia	42	(20)
Thrombocytopenia	29	(14)
Gastrointestinal Disorder		
Abdominal Pain	23	(11)
Constipation	20	(10)
Diarrhea	61	(29)
Nausea	56	(27)
Vomiting	28	(13)
General Disorders and Administration Site Conditions		
Asthenia	20	(10)
Catheter Site erythema	20	(10)
Chills	22	(10)
Mucosal inflammation	29	(14)
Edema Peripheral	33	(16)
Pyrexia	59	(28)
Metabolism and Nutrition Disorders		
Hypokalemia	46	(22)

Body System Preferred Term	Posaconazole Tablet (300 mg) (n=210)	
Hypomagnesemia	20	(10)
Nervous System Disorders		
Headache	30	(14)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	35	(17)
Epistaxis	30	(14)
Skin and Subcutaneous Tissue Disorders		
Rash	34	(16)
Vascular Disorders		
Hypertension	23	(11)

Clinical Laboratory Values

In (uncontrolled) trials of patients with invasive fungal infections treated with NOXAFIL oral suspension doses of 800 mg/day, the incidence of clinically significant liver function test abnormalities was: ALT and AST (> 3 X Upper Limit Normal {ULN}) 11 % and 10 %, respectively; total bilirubin (> 1.5 X ULN) 22 %; and alkaline phosphatase (> 3 X ULN) 14 %. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with higher plasma concentrations of posaconazole. In patients, the majority of abnormal liver function tests results showed minor and transient changes and rarely led to discontinuation of therapy.

In the comparative trials of patients infected with HIV treated with NOXAFIL at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows: ALT and AST (> 3 X ULN) 3 % and 6 %, respectively: total bilirubin (> 1.5 X ULN) 3 %; and alkaline phosphatase (> 3 X ULN) 3 %.

The number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at Baseline to Grade 3 or 4 during the study are presented in Table 15 for the prophylaxis studies 316 and 1899.

Table 15: Studies: Posaconazole oral suspension studies 316 and 1899, Changes in Liver Function Test Results from CTC Grade 0, 1 or 2 at Baseline to Grade 3 or 4.

Oral suspension Study 316	**Number (%) of Patients With Change[a]**	
Laboratory Parameter	Posaconazole N=301	Fluconazole N=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)

Oral suspension Study 1899		
	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

[a] Change from Grade 0 to 2 at Baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

DOSAGE AND ADMINISTRATION

NOXAFIL Oral Suspension should be administered with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal.

NOXAFIL Modified Release Tablets should be swallowed whole, and not be divided, crushed, or chewed. NOXAFIL Modified Release Tablets may be taken without regard to food intake.

Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections (see Interactions with other medicines).

Non-Interchangeability between NOXAFIL Modified Release Tablets and NOXAFIL Oral Suspension

The prescriber should follow the specific dosing instructions for each formulation. The modified release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations.

Administration instructions for NOXAFIL Oral Suspension

Shake well before use.

Refractory Invasive Fungal Infections (IFI) / Intolerant Patients with IFI: NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day with a meal or 240 mL of nutritional supplement. Dividing the dose further to 200 mg (5 mL) four times a day has been shown to enhance exposure to posaconazole, particularly in patients who have limited oral intake. Increasing the total daily dose above 800 mg does not further enhance the exposure to posaconazole (See Pharmacology).

Oropharyngeal Candidiasis in HIV-infected patients: NOXAFIL should be administered as a loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.

Oropharyngeal Candidiasis refractory to Itraconazole or Fluconazole in HIV-infected patients: NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day.

Prophylaxis of Invasive Fungal Infections: NOXAFIL should be administered at a dose of 200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Each dose of NOXAFIL oral suspension should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food, to enhance exposure.

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

Administration instructions for NOXAFIL Modified Release Tablets

Refractory Invasive Fungal Infections (IFI) / Intolerant Patients with IFI: Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Prophylaxis of Invasive Fungal Infections: Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

NOXAFIL modified release tablets can be taken without regard to food intake.

Use in renal impairment: No dose adjustment is required for renal dysfunction and as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (See Pharmacology). Due to variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (See Pharmacology).

Use in hepatic impairment: There is limited pharmacokinetic data in patients with hepatic impairment; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic impairment, there was an increase in half-life with a decrease in hepatic function (See Pharmacology).

Use in Paediatrics: Safety and efficacy in adolescents and children below the age of 13 years have not been established.

Use in the Elderly: No dosage adjustment is recommended for elderly patients (See Pharmacology).

OVERDOSAGE

During clinical trials, patients who received posaconazole oral suspension doses up to 1600 mg/day had no noted adverse reactions different from those reported with patients at the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg posaconazole oral suspension twice a day for 3 days. No adverse reactions were noted by the investigator.

In a trial of patients with severe haemodialysis-dependent renal dysfunction (Cl_{cr} < 20 mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

There is no experience with overdosage of posaconazole modified release tablets.

Contact the Poisons Information Centre on 131126 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

NOXAFIL ORAL SUSPENSION contains 40 mg posaconazole per mL of suspension. NOXAFIL oral suspension 105 mL is packaged in a 123 mL amber Ph. Eur. Type IV

glass bottle, closed with a plastic child-resistant closure. A measuring spoon, composed of clear polystyrene and graduated to measure 2.5 mL or 5 mL of the suspension, is provided with each bottle. Shake well before use. Store below 25°C. Do not freeze.

NOXAFIL MODIFIED RELEASE TABLETS 100 mg are available as yellow, coated, capsule-shaped tablets, debossed with “100” on one side. NOXAFIL Modified Release Tablets are available in blister packs of 24 and 96 tablets.

Store NOXAFIL Modified Release Tablets below 30°C. Store in original container.

NOXAFIL Oral Suspension: AUST R 115556

NOXAFIL Modified Release Tablets: AUST R 216283

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited

Level 1, Building A, 26 Talavera Road

Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

All states and ACT – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

15 March 2006

DATE OF MOST RECENT AMENDMENT

29 September 2017

1.6.2.2.3.2　　静注用濃厚溶液

2018年10月版の添付文書を添付する。

（Australia_POS_IV_20181003.pdf）

Confidential

AUSTRALIAN PRODUCT INFORMATION

NOXAFIL®

(posaconazole)
Concentrated Injection

1 NAME OF THE MEDICINE

Posaconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Posaconazole is a white to off-white crystalline powder. It has a melting range of 164°C - 165°C and is insoluble in water.

Each vial of NOXAFIL concentrated injection contains 300 mg of posaconazole (18 mg per mL).

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

NOXAFIL (posaconazole) concentrated injection is a clear, colourless to yellow liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NOXAFIL (posaconazole) concentrated injection is indicated for use in the treatment of the following invasive fungal infections in adults:

- Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy.
- Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.

NOXAFIL is also indicated for the:

- Prophylaxis of invasive fungal infections among adults, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Recommended dose is shown in Table 1.

TABLE 1. Recommended dose according to indication

Indication	Dose and duration of therapy
Refractory invasive fungal infections (IFI)/intolerant to alternative therapy	Loading dose of 300 mg NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Indication	Dose and duration of therapy
Prophylaxis of invasive fungal infections	Loading dose of 300 mg NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or MDS, prophylaxis with NOXAFIL should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.

Method of administration
NOXAFIL concentrated injection must be diluted before administration. Not for bolus injection.

- Equilibrate the refrigerated vial of NOXAFIL to room temperature.
- Aseptically transfer 16.7 mL of posaconazole to an IV bag (or bottle) containing a compatible infusion solution (see below for list of diluents) using a volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes. Not for IV bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes. **Note: In clinical trials, multiple peripheral infusions given through the same vein were not well tolerated (see Section 4.8 Adverse Effects (Undesirable Effects)).**
- NOXAFIL is a single dose unpreserved sterile solution. Therefore, from a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2°-8°C. NOXAFIL is for single use only and any unused solution should be discarded.

NOXAFIL concentrated injection can be diluted with:

5 % dextrose in water
0.9 % sodium chloride
0.45% sodium chloride
5% dextrose and 0.45% sodium chloride
5% dextrose and 0.9% sodium chloride
5% dextrose and 20 mEq KCl

NOXAFIL concentrated injection should only be administered with these diluents.

NOXAFIL concentrated injection must not be diluted with Lactated Ringer's solution, 5% dextrose with Lactated Ringer's solution, 4.2% sodium bicarbonate.

Intravenous line compatibility
A study was conducted to evaluate physical compatibility of NOXAFIL concentrated injection with injectable drug products and commonly used intravenous diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity.

Based on the results of the study, the following drug products can be infused at the same time through the same intravenous line (or cannula) as NOXAFIL concentrated injection:

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulphate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Any products not listed in the table above should not be co-administered with NOXAFIL through the same intravenous line (or cannula).

NOXAFIL concentrated injection should be inspected visually for particulate matter prior to administration. The solution of NOXAFIL ranges from colourless to pale yellow. Variations of colour within this range do not affect the quality of the product.

Use in renal impairment: In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection for IV infusion should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrated injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to NOXAFIL oral suspension therapy. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.4 Special Warnings and Precautions for Use**).

Use in hepatic impairment: There is limited pharmacokinetic data in patients with hepatic insufficiency; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic insufficiency, there was an increase in half-life with a decrease in hepatic function (see **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations).**

Use in paediatrics: Safety and efficacy in children below the age of 18 years have not been established.

NOXAFIL concentrated injection should not be used in children because of pre-clinical safety concerns (see **Section 4.4 Special Warnings and Precautions for Use, Pre-clinical safety**).

Use in the elderly: No dosage adjustment is recommended for elderly patients (see **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations**).

4.3 CONTRAINDICATIONS

NOXAFIL is contraindicated in patients with known hypersensitivity to posaconazole or to any of the excipients.

Coadministration of posaconazole and ergot alkaloids (ergotamine, dihydroergotamine) is contraindicated as posaconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolised through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

Although not studied *in vitro* or *in vivo*, coadministration of posaconazole and certain drugs metabolised through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozide, and quinidine may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles. Subjects with severe or serious reactions to azoles were excluded from key studies of posaconazole.

Hepatic toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalized without interruption of therapy and rarely required drug discontinuation. Rarely, more severe hepatic reactions (including cases that have progressed to fatal outcomes) were reported in patients with serious underlying medical conditions (e.g. haematological malignancy) during treatment with posaconazole. In the clinical pharmacology program, no healthy subject had CTC Grade 3 or Grade 4 (>5 x ULN) elevations in their liver function test results. Most of these LFT changes were mild in severity and all were transient in nature, returned to baseline after the cessation of dosing, and rarely led to study discontinuation. See Table 2 for hepatic enzyme abnormalities in healthy volunteers.

Liver function tests should be evaluated at the start of and during the course of posaconazole therapy, particularly in treatment beyond 14 days with posaconazole concentrated injection. Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole should be considered if clinical signs and symptoms are consistent with development of liver disease.

TABLE 2. Summary of Hepatic Enzyme Abnormalities in the Healthy Volunteers

CTC Grade	AST	ALT	GGT

	POS n=444	Placebo n=48	POS n=444	Placebo n=48	POS n=431	Placebo n=47
0 (≤1 x ULN)	417 (94%)	48 (100%)	388 (87%)	46 (96%)	408 (95%)	46 (98%)
1 (>1 - 2.5 x ULN)	26 (6%)	0 (0%)	50 (11%)	1 (2%)	20 (5%)	1 (2%)
2 (>2.5 - 5 x ULN)	1 (<1%)	0 (0%)	6 (1%)	1 (2%)	3 (1%)	0 (0%)

CTC=Common Toxicity Criteria; ULN=upper limit of normal
Note: The majority of subjects had CTC Grade 0 liver function test (LFTs) at baseline. This table summarizes the worst CTC grade observed during the treatment phase per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included in the summary.

QT prolongation

Some azoles have been associated with prolongation of the QT_c interval on the electrocardiogram (ECG). Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with medicines that are known to prolong the QT_c interval and are metabolised through the CYP3A4 (See **Section 5.2 Pharmacokinetic Properties, Electrocardiogram evaluation**, **Section 4.3 Contraindications**, **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Midazolam and other benzodiazepines metabolised by CYP3A4

Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam).

Dose adjustment of benzodiazepine metabolised by CYP3A4 should be considered (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Vincristine toxicity

Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).**

Effects on adrenal steroid hormones

As observed with other azole antifungal agents, effects related to inhibition of adrenal steroid hormone synthesis were seen in repeat-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Use in hepatic impairment

See **Section 4.4. Special Warnings and Precautions for Use, Hepatic toxicity** and **Section Section 4.2 Dose and Method of Administration, Use in hepatic impairment**.

Use in renal impairment

In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the

patient justifies the use of NOXAFIL concentrated injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to NOXAFIL oral suspension therapy.

Due to the variability in exposure, patients with severe renal impairment (eGFR: <20 mL/min/1.73 m^2) should be monitored closely for breakthrough fungal infections (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration).**

A specific study has not been conducted with posaconazole concentrated injection.

Following single-dose administration of 400 mg of the oral suspension, there was no effect of mild and moderate renal impairment (n=18, eGFR ≥20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, eGFR < 20 mL/min/1.73 m^2), the exposure of posaconazole was highly variable (96 % CV) compared to the exposure in the other renal groups (40 % CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected. Posaconazole is not removed by haemodialysis.

Use in the elderly

Of the 279 patients treated with posaconazole concentrated injection, 52 (19%) were greater than 65 years of age. The pharmacokinetics of posaconazole concentrated injection are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients and age was not a significant covariate in the population PK model; therefore, no dosage adjustment is recommended for NOXAFIL concentrated injection in geriatric patients.

Paediatric use

(See **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Children (<18 years)**). Safety and effectiveness in paediatric patients below the age of 18 years have not been established.

NOXAFIL concentrated injection should not be used in children because of pre-clinical safety concerns (see **Section 5.3 Preclinical Safety Data, Pre-clinical safety**).

Effects on laboratory tests

See **Section 4.8 Adverse Effects (Undesirable Effects), Clinical laboratory values**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Summary of drug interactions

Contraindicated	Avoid concomitant use unless the benefit outweighs the risk	Dose adjustment of other medications and/or monitoring of adverse events	No dose adjustment required
Ergotamine or dihydroergotamine	Rifabutin	Rifabutin	Antacids
Terfenadine, astemizole	Phenytoin	Cyclosporine	Zidovudine, ritonavir, lamivudine, indinavir

Cisapride	Cimetidine	Tacrolimus	Glipizide
Pimozide	Efavirenz	Sirolimus	
Quinidine	Vinca alkaloids		
Halofantrine		Midazolam	
HMG-CoA reductase inhibitors primarily metabolized through CYP3A4		Atazanavir/ritonavir Fosamprenavir	
		Calcium channel blockers metabolized through CYP3A4	
		Sulfonylureas	
		Digoxin	

Note that the majority of the interaction studies were carried out in healthy volunteers with repeat dose regimens of posaconazole 400 mg (oral suspension) twice daily administered with a meal or nutritional supplement. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole concentrated injection as well. See below for further information.

Effect of other drugs on posaconazole
Posaconazole is metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations.

Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole by 43 % and 49 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk.

Cimetidine (400 mg twice a day) decreased the C_{max} and AUC of posaconazole 200 mg once a day each by 39 %. Concomitant use of posaconazole and cimetidine should be avoided unless the benefit outweighs the risk. The effect of other H_2 receptor antagonists and proton pump inhibitors that may suppress gastric acidity has not been studied. Reduction in bioavailability may occur, therefore co-administration of posaconazole with H_2 receptor antagonists and proton pump inhibitors should be avoided if possible.

Antacids (20 mL single dose of liquid antacid equivalent to 25.4 mEq acid neutralizing capacity/5mL) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Gastrointestinal Motility Agents: No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when oral posaconazole was concomitantly administered with metoclopramide. No dosage adjustment is required when given concomitantly with metoclopramide.

Glipizide: (10 mg single dose) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Ritonavir (600 mg twice a day) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Efavirenz: (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45% and 50%, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. A study conducted in 20 healthy volunteers, repeat dose administration of fosamprenavir (700 mg twice a day for 10 days) decreased the C_{max} and AUC of posaconazole (200 mg once a day on the 1st day, 200 mg twice a day on the 2nd day, then 400 mg twice a day for 8 days) by 21% and 23%, respectively. The GMRs of posaconazole C_{max} and AUC when taken as posaconazole versus posaconazole/fosamprenavir were 0.79 (0.71-0.89) and 0.77 (0.68-0.87), respectively.

Effects of posaconazole on other drugs
Posaconazole is not metabolised to a clinically significant extent through the cytochrome P450 system. However, posaconazole is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolised through this enzyme pathway may increase when administered with posaconazole.

Terfenadine, astemizole, cisapride, pimozide, and quinidine: Although not studied *in vitro* or *in vivo,* co-administration of posaconazole and certain drugs such as terfenadine, astemizole, cisapride, pimozide, and quinidine, metabolized through the CYP3A4 system may result in increased plasma concentrations of these drugs, leading to potentially serious and/or life threatening adverse events (QT prolongation and rare occurrences of torsade de pointes). Therefore, co-administration of these drugs with posaconazole is contraindicated (see **Section 4.3 Contraindications**).

Ergot alkaloids: Although not studied *in vitro* or *in vivo,* posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Coadministration of posaconazole and ergot alkaloids is contraindicated (see **Section 4.3 Contraindications**).

Vinca alkaloids: Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see **Section 4.4 Special Warnings and Precautions for Use**). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Cyclosporine: In heart transplant patients on stable doses of cyclosporine, posaconazole 200 mg once daily increased cyclosporine concentrations requiring dose reductions. Cases of elevated cyclosporine levels resulting in serious adverse events, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving cyclosporine, the dose of cyclosporine should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of cyclosporine should be adjusted as necessary.

Tacrolimus: Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9 fold, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during coadministration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

Rifabutin: Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If the drugs are coadministered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam and other benzodiazepines metabolised by CYP3A4: In a study in healthy volunteers posaconazole oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole oral suspension 400 mg twice daily for 7 days increased the intravenous midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, posaconazole oral suspension (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during coadministration.

Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) (see **Section 4.4 Special Warnings and Precautions for Use**).

Zidovudine (AZT), lamivudine (3TC), ritonavir, indinavir: In HIV infected patients on stable doses of zidovudine (300 mg twice a day or 200 mg every 8 hours), lamivudine (150 mg twice a day), ritonavir (600 mg twice a day) and/or indinavir (800 mg every 8 hours), posaconazole had no clinically significant effect on the C_{max} and AUC of these medicinal products. Although not considered clinically significant, ritonavir exposure was increased by 30% with the addition of posaconazole.

HMG-CoA reductase inhibitors primarily metabolized through CYP3A4: Repeat dose administration of oral posaconazole (50, 100, and 200 mg once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased statins concentrations in plasma can be associated with rhabdomyolysis. Co-administration of posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated.

Interactions with HMG-CoA reductase inhibitors that are not metabolized by CYP3A4 have not been investigated but clinically relevant drug interactions are not expected as posaconazole does not inhibit other CYP isoenzymes at relevant concentrations.

Calcium channel blockers metabolized through CYP3A4: Although not studied *in vitro* or *in vivo,* frequent monitoring for adverse effects and toxicity related to calcium channel blockers is recommended during coadministration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin: Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas: Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

HIV Protease Inhibitors: As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir (300 mg once a day for 7 days) an average of 2.6-fold and 3.7-fold, respectively, in healthy subjects. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir to a lesser extent when administered as a boosted regimen with ritonavir (300 mg atazanavir plus ritonavir 100 mg once a day for 7 days) with an average of 1.5-fold and 2.5-fold, respectively, in healthy subjects. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Fosamprenavir: The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown. A study conducted in 20 healthy subjects, administration of posaconazole (200 mg once a day on the 1st day, 200 mg twice a day on the 2nd day, then 400 mg twice a day for 8 days) with fosamprenavir (700 mg twice a day for 10 days) resulted in a 36 % and 65 % lower C_{max} and AUC for amprenavir compared to when fosamprenavir was administered with ritonavir. The GMRs of amprenavir C_{max} and AUC when taken as fosamprenavir and posaconazole versus fosamprenavir/ritonavir were 0.64 (0.55-0.76) and 0.35 (0.32-0.39), respectively.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Posaconazole administered by the oral route had no effect on the fertility of male rats at doses up to 180 mg/kg/day (2.8 times the exposure achieved from a 300 mg IV dose in humans). Posaconazole administered by the oral route to female rats at doses up to 45 mg/kg/day (3.4 times the exposure from a 300 mg IV dose in patients) for 2 weeks prior to mating did not affect fertility, but disruption of oestrus cycling was seen in female rats treated for 4 weeks.

Use in pregnancy

Pregnancy Category B3 - There are no adequate studies in pregnant women. A total of three pregnancies have been reported in female subjects treated with posaconazole oral suspension. Two pregnancies were electively terminated; no examination was reported on the foetuses. Another pregnancy was diagnosed at a follow-up visit approximately 1 month after the completion of a full 16-week prophylactic treatment with POS oral suspension 200 mg TDS in a patient who had received an allogeneic haematopoietic stem cell transplant. The subject delivered a healthy full-term male infant via caesarean section.

Studies in rats with posaconazole administered by the oral route have shown reproductive toxicity including post implantation loss, increased skeletal variations, teratogenicity (craniofacial malformations), increased gestation length, dystocia, and reduced postnatal viability at exposure levels lower than those expected at the recommended doses in humans. An increase in post implantation loss and increased skeletal variations were seen in rabbits at plasma exposure levels greater than those of humans receiving therapeutic doses of posaconazole oral suspension.

NOXAFIL must not be used during pregnancy unless the benefit to the mother clearly outweighs the risk to the foetus. Women of childbearing potential must be advised to always use effective contraceptive measure during treatment and for at least 2 weeks after completing therapy.

Use in lactation

Posaconazole administered by the oral route is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Women taking posaconazole should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Posaconazole concentrated injection
In clinical trials, the type and frequency of adverse effects reported for posaconzole concentrated injection were generally similar to that reported in trials of posaconazole oral suspension.

In initial studies of healthy volunteers, administration of a single dose of posaconazole concentrated injection infused over 30 minutes via a peripheral venous catheter was well tolerated. However, multiple doses of posaconazole concentrated injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, posaconazole concentrated injection was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter.

The safety of posaconazole concentrated injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole concentrated injection when given as antifungal prophylaxis (Study 5520). Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range 18-82 years, 19% of patients were ≥65 years of age), and were 95% white and 8% Hispanic. Ten patients received a single dose of 200 mg posaconazole concentrated injection, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. Each patient in the multiple dose cohorts received BD dosing on Day 1. In each cohort, following posaconazole IV therapy, patients received posaconazole oral suspension to complete 28 days of total posaconazole therapy. Safety and efficacy of posaconazole concentrated injection at the recommended dose has not been assessed beyond 14 days in clinical trials.

Table 3 presents treatment-emergent adverse reactions observed in patients treated with posaconazole IV solution 300 mg daily dose at an incidence of ≥10% in the posaconazole concentrated injection study.

TABLE 3. **Posaconazole concentrated injection (Study 5520): Number (%) of Subjects Treated with Posaconazole IV Solution 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%**

Body System **Preferred Term**	**Posaconazole IV Solution Treatment Phase n=237 (%)***		**Posaconazole IV Solution Treatment Phase or Subsequent Oral Suspension Treatment Phase n=237(%)†**	
Subjects Reporting any Adverse Reaction	220	(93)	235	(99)
Blood and Lymphatic System Disorder				
Anemia	16	(7)	23	(10)
Febrile Neutropenia	44	(19)	54	(23)
Thrombocytopenia	17	(7)	25	(11)
Gastrointestinal Disorder				
Abdominal Pain Upper	15	(6)	25	(11)
Abdominal Pain	30	(13)	41	(17)
Constipation	18	(8)	31	(13)
Diarrhoea	75	(32)	93	(39)
Nausea	46	(19)	70	(30)
Vomiting	29	(12)	45	(19)
General Disorders and Administration Site Conditions				
Fatigue	19	(8)	24	(10)
Chills	28	(12)	38	(16)
Mucosal Inflammation	37	(16)	44	(19)
Edema Peripheral	28	(12)	35	(15)
Pyrexia	49	(21)	73	(31)
Metabolism and Nutrition Disorders				
Decreased appetite	23	(10)	29	(12)
Hypokalemia	51	(22)	67	(28)
Hypomagnesemia	25	(11)	30	(13)
Nervous System Disorders				
Headache	33	(14)	49	(21)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	21	(9)	31	(13)

Dyspnea	16	(7)	24	(10)
Epistaxis	34	(14)	40	(17)
Skin and Subcutaneous Tissue Disorders				
Petechiae	20	(8)	24	(10)
Rash	35	(15)	56	(24)
Vascular Disorders				
Hypertension	20	(8)	26	(11)
*Adverse reactions reported in patients with an onset during the posaconazole IV dosing phase of the study. †Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of posaconazole therapy.				

The most frequently reported adverse effect (>30%) with an onset during the posaconazole IV phase of dosing with 300 mg once daily was diarrhoea (32%).

The most common adverse effect (>1%) leading to discontinuation of posaconazole IV solution 300 mg once daily was acute myelogenous leukemia (AML) (1%).

Posaconazole oral suspension
Drug-related, adverse reactions observed in 2400 subjects dosed with posaconazole oral suspension are shown in Table 4. 172 patients received posaconazole oral suspension therapy for ≥ 6 months; 58 of these received posaconazole oral suspension therapy for ≥ 12 months.

The most frequently reported adverse reactions reported across the whole population of healthy volunteers and patients were nausea (6%) and headache (6%).

TABLE 4. Treatment-related adverse reactions reported in posaconazole dosed subjects by body system and frequency n=2400
Common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000)

Infections and infestations Uncommon: Rare:	 oral candidiasis, sinusitis catheter related infection, non herpetic cold sores, oesophageal candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders Common: Uncommon: Rare:	 neutropenia anaemia, thrombocytopenia, leukopenia, eosinophilia, lymphadenopathy abnormal blood gases, haemolytic uraemic syndrome, neutrophilia, pancytopenia, coagulation disorder, haemorrhage NOS, platelet count increased, prothrombin decreased, prothrombin time prolonged, purpura, thrombotic thrombocytopenic purpura
Immune system disorders Uncommon: Rare:	 allergic reaction hypersensitivity reaction, Stevens Johnson syndrome

Endocrine disorders	
Rare:	adrenal insufficiency, gonadotropins decreased
Metabolism and nutrition disorders	
Common:	anorexia, electrolyte imbalance
Uncommon:	hyperglycaemia, hypertriglyceridaemia, hyperuricaemia, weight decrease, LDH increased, dehydration
Rare:	amylase increased, hypercholesterolemia, hyperlipaemia, hyperproteinaemia, hypoalbuminaemia, lipase increased, metabolic acidosis, renal tubular acidosis, vitamin K deficiency, weight increase
Psychiatric disorders	
Uncommon:	altered mental status, anxiety, confusion, insomnia
Rare:	amnesia, depression, abnormal dreaming, emotional lability, libido decreased, paroniria, psychosis
Nervous system disorders	
Common:	dizziness, headache, paresthesia, somnolence
Uncommon:	neuropathy, hypoesthesia, convulsions, tremor
Rare:	peripheral neuropathy, areflexia, ataxia, cognition impaired, delirium, dysphonia, dystonia, encephalopathy, hemiparesis, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, impaired concentration, memory impairment, meningism, mononeuritis, restless leg syndrome, sciatica, syncope
Eye disorders	
Uncommon:	conjunctivitis, blurred vision
Rare:	eye pain, eyes dry, periorbital oedema, diplopia, photophobia, scotoma
Ear and labyrinth disorder	
Uncommon:	earache, vertigo
Rare:	hearing impairment, tinnitus
Cardiac disorders	
Uncommon:	abnormal ECG, QTc/QT prolongation, atrial flutter, atrial fibrillation, bundle branch block, tachycardia, extrasystoles, palpitation, ventricular hypertrophy
Rare:	bradycardia, cardiac failure, cardio-respiratory arrest, sudden death, ventricular tachycardia, aortic valve sclerosis, cardiomegaly, ejection fraction decreased, mitral valve disease NOS, myocardial infarction, supraventricular tachycardia, premature atrial contractions, premature ventricular contractions, AV block, torsades de pointes
Vascular disorders	
Uncommon:	flushing, hot flushes, hypertension, hypotension
Rare:	atherosclerosis, cerebrovascular accident, deep venous thrombosis NOS, pulmonary embolism, ischemia, haematoma
Respiratory, thoracic and mediastinal disorders	
Uncommon:	chest pain, coughing, dyspnoea, epistaxis,

Rare:	pharyngitis, nasal congestion atelectasis, dry throat, pulmonary hypertension, interstitial pneumonia, nasal irritation, pneumonitis, postnasal drip, pulmonary infiltration, rales, rhinitis, rhinorrhoea
Gastrointestinal disorders Common: Uncommon: Rare:	 abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting taste perversion, constipation, loose stools, abdominal distention, dysphagia, ascites, eructation, thirst, gastritis, gastroesophageal reflux, mucositis NOS, oesophagitis, pancreatitis, tongue discolouration gastrointestinal tract haemorrhage, ileus, abdominal tenderness, cheilitis, haemorrhagic diarrhoea, oesophagus ulceration, haemorrhagic gastritis, odynophagia, pancreatic enzymes NOS increased, proctalgia, retching, aphthous stomatitis, tenesmus, melena, gingivitis, glossitis
Hepatobiliary disorders Common: Uncommon: Rare:	 elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin) hepatitis, hepatocellular damage, hepatomegaly, jaundice asterixis, cholestasis, hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, splenomegaly
Skin and subcutaneous tissue disorders Common: Uncommon: Rare:	 rash alopecia, dry skin, maculopapular rash, urticaria, furunculosis, acne, mouth ulceration, pruritus, pruritic rash stomatitis, dermatitis, erythema, erythematous rash, follicular rash, macular rash, night sweats, seborrhoea, skin nodule, vesicular rash
Musculoskeletal and connective tissue disorders Uncommon: Rare:	 myalgia, arthralgia, back pain, musculoskeletal pain, flank pain, muscle weakness bone pain, chest wall pain, fasciitis, neck stiffness, cramps extremities, muscle cramps
Renal and urinary disorders Uncommon: Rare:	 albuminuria, altered micturition frequency, dysuria, increased blood creatinine, acute renal failure, renal failure, haematuria, renal impairment, nocturia increased BUN, interstitial nephritis, micturition disorder, renal calculus, urinary tract obstruction NOS
Reproductive system and breast disorders Uncommon: Rare:	 menstrual disorder leukorrhoea, breast pain
General disorders and administration site conditions	

Common: Uncommon: Rare:	asthenia, fatigue, fever increased sweating, pain, rigors, malaise, weakness, oedema, tooth discolouration face oedema, tongue oedema
Investigations Uncommon:	 altered drug levels
Injury, poisoning and procedural complications Uncommon: Rare:	 drug toxicity (NOS) ecchymoses

Serious adverse events that were considered treatment related were reported in 8% (35/428) of patients in the refractory invasive fungal infection pool. Most individual treatment related serious adverse events were reported by <1% of patients and are largely reflective of the serious underlying conditions that predisposed to the development of the invasive fungal infection. Treatment related serious adverse events reported in 1 % of subjects (3 or 4 subjects each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting. Treatment-related serious adverse events reported in 605 patients treated with posaconazole oral suspension for prophylaxis (1% each) included bilirubinaemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with posaconazole oral suspension have included adrenal insufficiency, pancreatitis, allergic and/or hypersensitivity reactions.

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. A pooled analysis of 173 posaconazole oral suspension-dosed healthy volunteers utilizing time matched ECGs did not show a potential to prolong the QT interval. In addition, rare cases of torsade de pointes have been reported in patients taking posaconazole oral suspension.

In addition, rare cases of haemolytic uremic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

TABLE 5. Treatment-related adverse events reported in ≥ 1% of patients treated for invasive fungal infections with posaconazole oral suspension
(Severity as classified by the investigator)

Disorder	**Total (All) n=330 Number (%)**	**Total (Mild/Moderate) n=330 Number (%)**	**Total (Severe/Life-Threatening) n=330 Number (%)**
Body as a Whole-General			
anorexia	8 (2)	8 (2)	0
asthenia	4 (1)	4 (1)	0
chest pain	2 (1)	2 (1)	0
dizziness	7 (2)	6 (2)	1 (<1)
drug level altered	7 (2)	4 (1)	3 (1)
fatigue	7 (2)	6 (2)	1 (<1)
fever	3 (1)	3 (1)	0
headache	15 (5)	13 (4)	2 (1)
weakness	2 (1)	2 (1)	0
Cardiovascular, general			
cardio-respiratory	2 (1)	0	2 (1)

arrest			
ventricular hypertrophy	2 (1)	1 (<1)	1 (<1)
Central and Peripheral Nervous System			
confusion	3 (1)	3 (1)	0
convulsions	2 (1)	0	2 (1)
hyperreflexia	2 (1)	2 (1)	0
hypoesthesia	2 (1)	2 (1)	0
mental status, altered	2 (1)	2 (1)	0
paresthesia	6 (2)	6 (2)	0
somnolence	3 (1)	3 (1)	0
tremor	2 (1)	2 (1)	0
Blood and lymphatic system	6 (2)	4 (1)	2 (1)
anaemia	4 (1)	3 (1)	1 (<1)
Eye	4 (1)	3 (1)	1 (<1)
vision blurred	2 (1)	2 (1)	0
Reproductive system and breast			
breast pain	1 (<1)	1 (<1)	0
menstrual disorder (based on females only)	2 (2)	2 (2)	0
Gastro-intestinal system			
abdominal distension	2 (1)	2 (1)	0
abdominal pain	16 (5)	13 (4)	3 (1)
constipation	2 (1)	2 (1)	0
diarrhoea	11 (3)	10 (3)	1 (<1)
dyspepsia	2 (1)	2 (1)	0
flatulence	3 (1)	3 (1)	0
mouth dry	5 (2)	5 (2)	0
nausea	31 (9)	2 (1)	29 (9)
vomiting	19 (6)	18 (5)	1 (<1)
Heart Rate and Rhythm			
atrial flutter	2 (1)	1 (<1)	1 (<1)
ECG abnormal specific	2 (1)	2 (1)	0
extrasystoles	2 (1)	1 (<1)	1 (<1)
fibrillation atrial	3 (1)	2 (1)	1 (<1)
QTc/QT prolongation	6 (2)	6 (2)	0
tachycardia	2 (1)	2 (1)	0
tachycardia supraventricular	2 (1)	1 (<1)	1 (<1)
Injury and poisoning			
drug toxicity (NOS)	2 (1)	0	2 (1)
Liver and biliary system			
bilirubinemia	4 (1)	3 (1)	1 (<1)
gamma-GT increased	2 (1)	0	2 (2)
hepatic enzymes increased	7 (2)	6 (2)	1 (<1)
hepatic function abnormal	2 (1)	2 (1)	0
jaundice	2 (1)	1 (<1)	1 (<1)

AST increased	9 (3)	6 (2)	3 (1)
ALT increased	11 (3)	9 (3)	2 (1)
Metabolic and nutritional			
phosphatase alkaline increased	6 (2)	5 (2)	1 (<1)
thirst	2 (1)	2 (1)	0
Musculo-skeletal system			
musculo-skeletal pain	2 (1)	2 (1)	0
Platelet, bleeding and clotting			
thrombocytopenia	2 (1)	2 (1)	0
Renal & Urinary System			
blood creatinine decreased	5 (2)	4 (2)	1 (<1)
nocturia	2 (1)	2 (1)	0
renal failure	2 (1)	1 (<1)	1 (<1)
renal failure acute	2 (1)	0	2 (1)
Skin / subcutaneous tissue			
alopecia	4 (1)	4 (1)	0
dry skin	3 (1)	3 (1)	0
pruritus	3 (1)	3 (1)	0
rash	9 (3)	7 (2)	2 (1)
rash maculopapular	4 (1)	3 (1)	1 (<1)
rash vesicular	2 (1)	2 (1)	0

TABLE 6. Treatment-related, treatment-emergent adverse events (any grade): ≥ 2% of subjects (OPC) with posaconazole oral suspension

Adverse event	**Number (%) of subjects**		
	Controlled OPC pool		**Refractory OPC pool**
	POS n = 557	**FLU n = 262**	**POS n = 239**
Subjects reporting any adverse event[a]	**150 (27)**	**70 (27)**	**135 (56)**
Body as a whole – general disorders			
Anorexia	6 (1)	1 (< 1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Headache	16 (3)	5 (2)	18 (8)
Central and peripheral nervous system disorders			
Somnolence	4 (1)	5 (2)	3 (1)
Disorders of blood and lymphatic system	2 (< 1)	0 (0)	6 (3)
Anaemia	10 (2)	4 (2)	20 (8)
Neutropenia			
Gastro-intestinal system disorders			
Abdominal pain	10 (2)	8 (3)	12 (5)
Diarrhoea	19 (3)	13 (5)	26 (11)
Flatulence	6 (1)	0 (0)	11 (5)
Mouth dry	7 (1)	6 (2)	5 (2)
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Liver and biliary system disorders			
Hepatic enzymes increased	1 (< 1)	0 (0)	5 (2)

Hepatic function abnormal	3 (1)	4 (2)	0 (0)
Metabolic and nutritional disorders			
Phosphatase alkaline increased	3 (1)	3 (1)	5 (2)
Musculo-skeletal system disorders			
Myalgia	1 (< 1)	0 (0)	4 (2)
Platelet, bleeding and clotting disorders			
Thrombocytopenia	3 (1)	0 (0)	4 (2)
Psychiatric disorders			
Insomnia	3 (1)	0 (0)	6 (3)
Skin and subcutaneous tissue disorders			
Pruritus	6 (1)	2 (1)	5 (2)
Rash	8 (1)	4 (2)	10 (4)

[a] number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

TABLE 7. Studies 316 and 1899, Treatment-related, treatment-emergent adverse events: All (≥ 2% incidence) and Severe/Life Threatening Number (%) of Subjects (Prophylaxis) in the posaconazole oral suspension or fluconazole treatment groups.

	POS n=605		FLU n=539		ITC n=58	
	All	**Severe/LT**	**All**	**Severe/LT**	**All**	**Severe/LT**
Subjects reporting any adverse event[a]	209 (35)	81 (13)	186 (35)	53 (10)	30 (52)	6 (10)
Gastro-Intestinal System Disorders						
Abdominal Pain	13 (2)	1 (< 1)	15 (3)	2 (< 1)	1 (2)	0
Constipation	4 (1)	0	12 (2)	0	0	0
Diarrhoea	28 (5)	4 (1)	24 (4)	1 (<1)	9 (16)	0
Dyspepsia	8 (1)	1 (<1)	9 (2)	0	0	0
Nausea	44 (7)	5 (1)	45 (8)	1 (<1)	8 (14)	0
Vomiting	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
Heart Rate and Rhythm Disorders						
QTc/QT Prolongation	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
Liver and Biliary System Disorders						
Bilirubinemia	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT Increased	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
Hepatic Enzymes Increased	15 (2)	11 (2)	10 (2)	3 (1)	0	0
SGOT Increased	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
SGPT Increased	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	1 (2)
Metabolic and Nutritional Disorders						
Hypokalemia	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders						
Rash	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

GGT = gamma glutamyl transpeptidase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

[a] number of subjects reporting treatment-emergent advserse events at least once during the study. Subjects may have reported more than one event.

Clinical laboratory values

In (uncontrolled) trials of patients with invasive fungal infections treated with NOXAFIL oral suspension doses of 800 mg/day, the incidence of clinically significant liver function test abnormalities was; ALT and AST (> 3 X Upper Limit Normal {ULN}) 11 % and 10 %, respectively; total bilirubin (> 1.5 X ULN) 22 %; and alkaline phosphatase (> 3 X ULN) 14 %. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with

higher plasma concentrations of posaconazole. In patients, the majority of abnormal liver function tests results showed minor and transient changes and rarely led to discontinuation of therapy.

In the comparative trials of patients infected with HIV treated with NOXAFIL at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows; ALT and AST (> 3 X ULN), 3 % and 6 %, respectively; total bilirubin (> 1.5 X ULN), 3 %; and alkaline phosphatase (> 3 X ULN), 3 %.

The number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at Baseline to Grade 3 or 4 during the study are presented in Table 8 for the prophylaxis studies 316 and 1899.

TABLE 8. Posaconazole oral suspension studies 316 and 1899, Changes in Liver Function Test Results from CTC Grade 0, 1 or 2 at Baseline to Grade 3 or 4.

	Number (%) of Patients With Change[a]	
Study 316		
Laboratory Parameter	Posaconazole N=301	Fluconazole N=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
Study 1899		
	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

a: Change from Grade 0 to 2 at Baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdosage of posaconazole concentrated injection.

During clinical trials, patients who received posaconazole oral suspension doses up to 1600 mg/day had no noted adverse reactions different from those reported with patients at the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg posaconazole oral suspension twice a day for 3 days. No adverse reactions were noted by the investigator.

In a trial of patients with severe haemodialysis-dependent renal dysfunction (Cl_{cr} < 20mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Antiinfective for systemic use, triazole derivative, J02AC04

Mechanism of action

Posaconazole is a triazole antifungal agent. It is an inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Ergosterol depletion, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and the function of some membrane-associated proteins. This results in the inhibition of cell growth and/or cell death.

Microbiology
Posaconazole has been shown *in vitro* and in clinical infections to be active against the following micro-organisms (see **Section 4.1 Therapeutic Indications):** *Aspergillus* species *(Aspergillus fumigatus, A. flavus, A. terreus, A. nidulans, A. niger, A. ustus, A. ochraceus), Candida* species *(Candida albicans, C. glabrata, C. krusei, C. parapsilosis), Cryptococcus neoformans, Coccidioides immitis, Fonsecaea pedrosoi, Histoplasma capsulatum, Pseudallescheria boydii* and species of *Alternaria, Exophiala, Fusarium, Ramichloridium, Rhizomucor, Mucor,* and *Rhizopus*. While posaconazole has been used in a clinical setting against these microorganisms, sufficient evidence for efficacy has not been collected for all the listed microorganisms (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis, C. famata, C. guilliermondii, C. lusitaniae, C. kefyr, C. rugosa, C. tropicalis, C. zeylanoides, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis, Cryptococcus laurentii, Kluyveromyces marxianus, Saccharomyces cerevisiae, Yarrowia lipolytica,* species of *Pichia*, and *Trichosporon, Aspergillus sydowii, Bjerkandera adusta, Blastomyces dermatitidis, Epidermophyton floccosum, Paracoccidioides brasiliensis, Scedosporium apiospermum, Sporothrix schenckii, Wangiella dermatitidis* and species of *Absidia, Apophysomyces, Bipolaris, Curvularia, Microsporum, Paecilomyces, Penicillium,* and *Trichophyton*. However, the safety and effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

NOXAFIL exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole,
- *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole,
- *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B),
- organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g. species of *Absidia, Mucor, Rhizopus* and *Rhizomucor)*.

In vitro NOXAFIL exhibited fungicidal activity against species of:

- *Aspergillus,*
- dimorphic fungi *(Blastomyces dermatitidis, Histoplasma capsulatum, Penicillium marneffei,*
- *Coccidioides immitis*)
- some species of *Candida.*

In animal infection models NOXAFIL was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Drug resistance
C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of $1x10^{-8}$ to $1x10^{-9}$. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active *in vitro* against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal drug combinations
When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. Clinical studies of posaconazole in combination with antifungal drugs including amphotericin B-based drugs and caspofungin have not been conducted.

Clinical trials

Posaconazole concentrated injection
Study 5520 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole concentrated injection.

Study 5520 enrolled a total of 279 subjects, including 268 receiving at least one dose of posaconazole concentrated injection. Cohort 0 was designed to evaluate the tolerability of a single dose of posaconazole concentrated injection when administered via a central line. Cohorts 1 and 2 of the study were designed to select a dose for further evaluation in Cohort 3, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Cohort 3 of the study was designed to evaluate posaconazole concentrated injection in a more diverse patient population, and to confirm the exposure of posaconazole concentrated injection in additional subjects at risk of a fungal infection.

The subject population for Cohorts 0, 1, and 2 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Cohorts 1 and 2: 200 mg BD on Day 1, followed by 200 mg QD thereafter (Cohort 1) and 300 mg BD on Day 1, followed by 300 mg QD thereafter (Cohort 2).

The subject population in Cohort 3 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Cohorts 1 and 2, all subjects in Cohort 3 received 300 mg BD on Day 1, followed by 300 mg QD thereafter.

The total subject population had a mean age of 51 years (range = 18-82 years), 95 % were White, the major ethnicity was not Hispanic or Latino (92 %), and 55 % were male. The study treated 155 (65 %) subjects with AML or MDS, and 82 (35 %) subjects with HSCT, as the primary diseases at study entry.

Serial pharmacokinetic samples were collected on Day 1 and at steady-state on Day 14 for all Cohort 1 and 2 subjects and on Day 10 for a subset of Cohort 3 subjects. This serial pharmacokinetic analysis demonstrated that 94 % of the subjects treated with the 300 mg QD dose attained steady state C_{av} between 500-2500 ng/mL. [C_{av} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours)]. This exposure was selected based on pharmacokinetic/pharmacodynamic considerations with posaconazole oral suspension. Subjects with AML/MDS with neutropenia following chemotherapy or HSCT subjects receiving immunosuppressive therapy to prevent or treat GVHD who received 300 mg QD achieved a mean C_{av} at steady state of 1500 ng/mL. The PK findings from the pivotal study (Study 5520) support a 300-mg daily dose of posaconazole concentrated injection for use in prophylaxis.

Posaconazole oral suspension studies
Invasive aspergillosis:
Efficacy in patients with refractory disease or intolerance to prior therapy: The efficacy and survival benefit of oral posaconazole for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations), itraconazole or, in a small number of cases, voriconazole or echinocandins, and/or with intolerance to amphotericin B (including liposomal formulations) or itraconazole was demonstrated in 107 patients enrolled in a salvage therapy trial. Patients were administered posaconazole 800 mg/day in divided doses for up to 585 days. The median duration of posaconazole therapy was 56 days (1-585 days).

The majority of patients were severely immunocompromised with underlying conditions such as haematologic malignancies, including bone marrow transplantation; solid organ transplantation; solid tumours and/or AIDS. An independent expert panel reviewed all patient data, including diagnosis of invasive aspergillosis, refractoriness and intolerance to previous therapy, and clinical outcome in a parallel and blinded fashion with an external control group of 86 patients treated with standard salvage therapy (e.g. amphotericin B including liposomal formulations, and/or itraconazole) mostly at the same time and at the same sites as the patients enrolled in the posaconazole trial.

A success was defined as either complete resolution (complete response) or a clinically meaningful improvement (partial response) of all signs, symptoms and radiographic findings attributable to the fungal infection. Stable, non-progressive disease and failure were considered to be a non-success. Most of the cases of aspergillosis were considered to be refractory in both the posaconazole group (88 %) and in the external control group (79 %) while the remaining patients were intolerant to prior antifungal therapy (12 % posaconazole; 21 % external control group).

As shown in Table 9, a successful global response at end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group (P=0.006).

TABLE 9. Overall efficacy of posaconazole at the end of treatment* for invasive aspergillosis in comparison to an external control group

	Posaconazole		**External Control Group**	
Overall Response	45/107 (42 %)		22/86 (26 %)	
	Adjusted Odds Ratio ** 4.06 (95 % CI: 1.50, 11.04) P=0.006			
	Unadjusted Odds ratio 2.11 (95 % CI: 1.14, 3.92) P=0.018			
Survival at day 365	**(38 %)**		**(22 %)**	
Success by Species				
All mycologically confirmed *Aspergillus* spp.***	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

* end of all study drug therapy plus 7 days within 372 days of the start of salvage therapy
** adjusted odds ratio was obtained using a logistic regression model adjusting for major covariates
*** includes other less common species or species unknown

Other serious fungal pathogens
Posaconazole has been shown to be effective against the following additional pathogens when other therapy had been ineffective or when the patient had developed intolerance of the prior therapy.

Zygomycosis: Successful responses to posaconazole therapy were noted in 7/13 (54%) of patients with zygomycete infections. Sites of infection included the sinuses, lung, and skin. Organisms included *Rhizopus*, *Mucor* and *Rhizomucor*. Most of the patients had underlying haematological malignancies, half of which required a bone marrow transplant. Half of the patients were enrolled with intolerance to previous therapy and the other half as a result of disease that was refractory to prior therapy. Three patients were noted to have disseminated disease, one of which had a successful outcome after failing amphotericin B therapy.

Fusarium *spp.*: Successful responses to posaconazole therapy were seen in 11 of 24 (46%) of patients with fusariosis. Four of the responders had disseminated disease and one patient had disease localized to the eye; the remainder had a variety of sites of infection. Seven of 24 patients had profound neutropenia at baseline. In addition, 3/5 patients with infection due to *F. solani* which is typically resistant to most antifungal agents, were successfully treated.

Chromoblastomycosis/mycetoma: Successful responses to posaconazole therapy were seen in 9 of 11 (82%) of patients with chromoblastomycosis or mycetoma. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis: The efficacy of posaconazole in the primary treatment of non-meningeal coccidioidomycosis was demonstrated in 15 clinically evaluable patients enrolled in an open label, non-comparative trial to receive posaconazole 400 mg daily for 6 months. Most patients were otherwise healthy and had infections at a variety of sites. A satisfactory response (defined as an improvement of at least 50 % of the Cocci score as defined by the BAMSG Coccidioidomycosis trial group) was seen in 12 of 15 patients (80 %) after an average of 4 months of posaconazole treatment. In a separate open-label, non-comparative trial, the safety and efficacy of posaconazole 400 mg twice a day was assessed in 16 patients with coccidioidomycosis infection refractory to standard treatment.

Most had been treated with amphotericin B (including lipid formulations) and/or itraconazole or fluconazole for months to years prior to posaconazole treatment. At the end of treatment with posaconazole, a satisfactory response (complete or partial resolution of signs and

symptoms present at baseline) as determined by an independent panel was achieved for 11/16 (69 %) of patients. One patient with CNS disease that had failed fluconazole therapy had a successful outcome following 12 months of posaconazole therapy.

Treatment of azole-susceptible oropharyngeal candidiasis (OPC) in HIV-infected patients

A randomised, double-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis. The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical and mycological response rates from the above study are shown in Table 10 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole demonstrated a significantly better mycological response rate than fluconazole 4 weeks after the end of treatment.

TABLE 10. Clinical Success Rates and Mycological Response Rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical Success Rate at Day 14	91.7 % (155/169)	92.5 % (148/160)
Clinical Success Rate 4 Weeks After End of Treatment	68.5 % (98/143)	61.8 % (84/136)
Mycological Response Rate 4 Weeks After End of Treatment*	40.6 % (41/101)	26.4 % (24/91)

*Statistically significant (P=0.0376)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

Mycological response rate was defined as mycological success (≤ 20 CFU/ml) divided by the total number of cases eligible for analysis.

Treatment of oropharyngeal candidiasis refractory to itraconazole and fluconazole (rOPC) in HIV-infected patients

The primary efficacy parameter in the short-term treatment study was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole 400 mg twice a day with an option for further treatment during a 3-month maintenance period. A 75 % (132/176) clinical success rate and a 36.5 % (46/126) mycological response rate (≤ 20 CFU/mL) were achieved after 4 weeks of posaconazole treatment. Clinical success rates ranged from 71 % to 100 %, inclusive, for all azole-resistant *Candida* species identified at Baseline, including *C. glabrata* and *C. krusei.*

In the long-term treatment study the primary efficacy endpoint was the clinical success rate (cure or improvement) after 3 months of treatment. A total of 100 HIV-infected patients with OPC and/or EC were treated with posaconazole 400 mg twice a day for up to 15 months. Sixty of these patients had been previously treated in Study 330. An 85.6 % (77/90) clinical success rate overall (cure or improvement) was achieved after 3 months of posaconazole treatment; 80.6 % (25/31) for previously untreated subjects.

The mean exposure to posaconazole based on the actual days dosed was 102 days (range: 1-544 days). Sixty-seven percent (67 %, 10/15) of patients treated with posaconazole for at least 12 months had continued clinical success at the last assessment.

Prophylaxis of invasive fungal infections (IFIs) (Studies 316 and 1899):

Two large, randomised, controlled studies were conducted using posaconazole as prophylaxis for the prevention of IFIs among patients at high risk.

Study 316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic HSCT recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medication + 7 days). The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole).

Study 1899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole).

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. There were significantly fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole or itraconazole. See Table 11 for results from both studies.

TABLE 11. Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections

Study 316: Allogeneic Hematopoietic Stem Cell Transplant Recipients with Graft vs. Host Disease			
	Posaconazole n =301	**Fluconazole n = 299**	**P-Value**
On therapy plus 7 days			
Clinical Failure	50 (17%)	55 (18%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	22 (7%)	0.0038
(*Aspergillus*)	3 (1%)	17 (6%)	0.0059
(*Candida*)	1 (<1%)	3 (1%)	
(Other)	3 (1%)	2 (1%)	
Through 16 weeks			
Clinical Failure	99 (33%)	110 (37%)	
Failure due to:			
Proven/Probable IFI	16 (5%)	27 (9%)	0.0740
(*Aspergillus*)	7 (2%)	21 (7%)	0.0013
(*Candida*)	4 (1%)	4 (1%)	
(Other)	5 (2%)	2 (1%)	
Study 1899: Neutropenic Patients with Acute Myelogenous Leukaemia/Myelodysplastic Syndromes			
	Posaconazole n =304	**Fluconazole/Itraconazole n = 298**	**P-Value**
On therapy plus 7 days			
Clinical Failure	82 (27%)	126 (42%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	25 (8%)	0.0009

(*Aspergillus*)	2 (1%)	20 (7%)	0.0001
(*Candida*)	3 (1%)	2 (1%)	
(Other)	2 (1%)	3 (1%)	
Through 100 days post-randomization			
Clinical Failure	158 (52%)	191 (64%)	
Failure due to:			
Proven/Probable IFI	14 (5%)	33 (11%)	0.0031
(*Aspergillus*)	2 (1%)	26 (9%)	<0.0001
(*Candida*)	10 (3%)	4 (1%)	
(Other)	2 (1%)	3 (1%)	

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) (Figure 1) as well as IFI-related deaths (P = 0.0209).

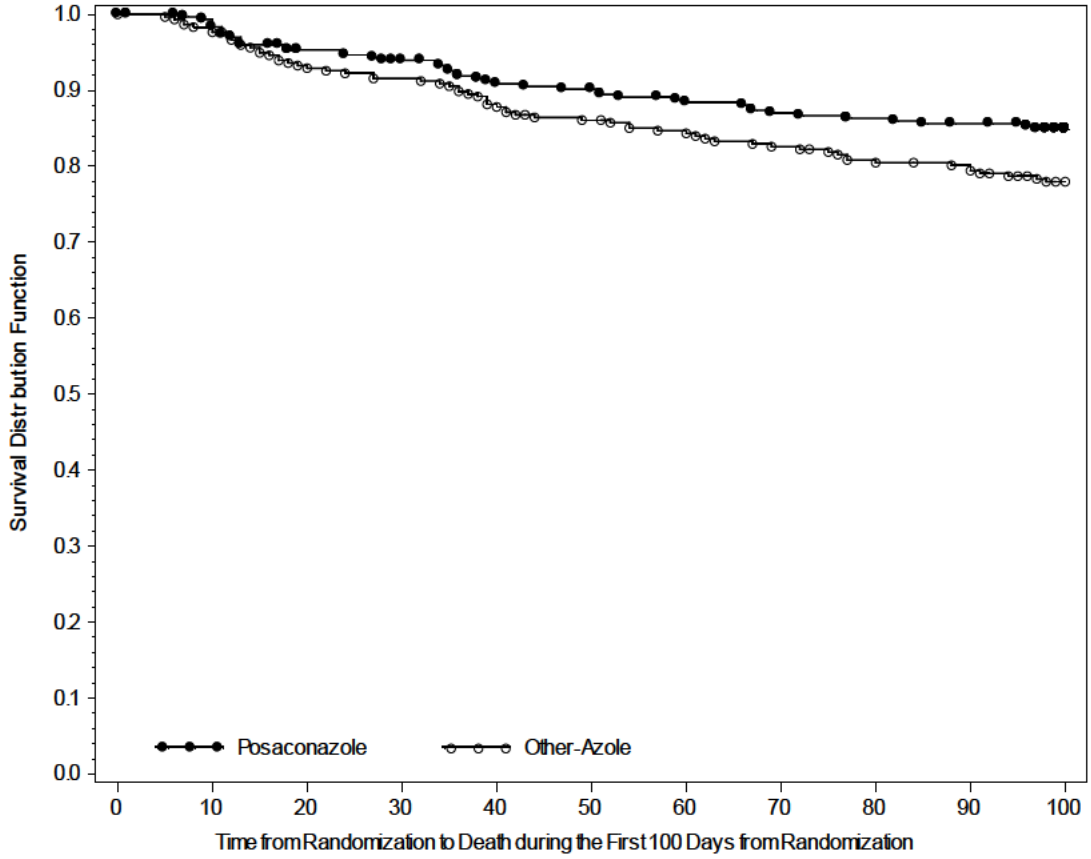


Figure 1. All cause mortality in Study 1899 (POS vs FLU/ITZ; P= 0.0354)

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Use in paediatric patients:
There is no paediatric experience for posaconazole concentrated injection.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic / pharmacodynamic relationships

A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see **Section 4.2 Dose and Method of Administration** on recommended dose regimens).

Distribution

Posaconazole exhibits dose proportional pharmacokinetics after single dosing in healthy volunteers and multiple dosing in patients in the therapeutic dose range (200-300 mg).

Following administration of 300 mg posaconazole concentrated injection, posaconazole has a distribution volume of 261 L, indicating extravascular distribution.

Posaconazole is highly protein bound (> 98.0 %), predominantly to serum albumin.

Metabolism

Posaconazole does not have any major circulating metabolites. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radio-labelled dose of posaconazole oral suspension.

Excretion

Posaconazole, after administration of 300 mg of posaconazole concentrated injection, is slowly eliminated with a mean half-life ($t_{1/2}$) of 27 hours and a mean clearance of 7.3 L/hr.

Posaconazole, after oral suspension administration, is slowly eliminated with a mean half-life ($t_{1/2}$) of 35 hours (range 20 to 66 hours) and an apparent total body clearance (Cl/F) of 32 L/hr. After administration of ^{14}C-posaconazole as oral suspension, posaconazole is predominantly excreted in the faeces (77 % of the radio-labelled dose) with the major component eliminated as parent drug (66 % of the radio-labelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radio-labelled dose excreted in urine (< 0.2 % of the radio-labelled dose is parent drug). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Summary of the mean pharmacokinetic parameters in patients
The pharmacokinetic parameters of posaconazole in patients following administration of posaconazole concentrated injection 300 mg once a day for 10 or 14 days following BD dosing on Day 1 are shown in Table 12.

TABLE 12. Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaconazole Concentrated injection (300 mg)*

Day	n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{interval}$ (ng*hr/mL)	C_{av} (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

$AUC_{interval}$ = area under the concentration-time curve over the dosing interval (i.e 24 hours);
C_{av}= $AUC_{interval}$;
C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max}=observed maximum plasma concentration; CV=coefficient of variation, expressed as a percent (%); Day=study day on treatment; T_{max}=time of observed maximum plasma concentration.
*300 mg dose administered over 90 minutes once a day following BD dosing on Day 1
†Median (minimum-maximum)

Pharmacokinetics in special populations
Children (< 18 years)

There is no paediatric experience with posaconazole concentrated injection (see **Section 5.3 Preclinical Safety Data, Pre-clinical safety** and **Section 4.2 Dose and Method of Administration**).

Gender
The pharmacokinetics of posaconazole concentrated injection are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Elderly
The pharmacokinetics of posaconazole concentrated injection are comparable in young and elderly subjects. No overall differences in safety were observed between geriatric patients and younger patients and age was not a significant covariant in the population PK model; therefore no dosage adjustment is recommended for geriatric patients.

Race
There is insufficient data among different races with posaconazole concentrated injection.

Weight
Pharmacokinetic modelling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Renal impairment
In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrated injection (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**). A specific study has not been conducted with posaconazole concentrated injection.

Following single-dose administration of 400 mg of the oral suspension, there was no effect of mild and moderate renal impairment (n=18, eGFR ≥20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, eGFR < 20 mL/min/1.73 m^2), the exposure of posaconazole was highly variable (96 % CV) compared to the exposure in the other renal groups (40 % CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected. Posaconazole is not removed by haemodialysis (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**).

Hepatic impairment
A specific study has not been conducted with posaconazole concentrated injection.

In a small number of subjects (n=12) studied with hepatic impairment (Child-Pugh class A, B or C) administered 200 mg posaconazole oral suspension, C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/mL for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/mL) for the normal subjects were consistent with previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26.6, 35.3, and 46.1 hours for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22.1 hours). Due to the limited pharmacokinetic data in patients with hepatic impairment; no recommendation for dose adjustment can be made.

Similar recommendations apply to posaconazole concentrated injection; however, a specific study has not been conducted with posaconazole concentrated injection.

Electrocardiogram evaluation
Multiple, time-matched ECGs collected over a 12 hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 85 years of age) administered posaconazole oral suspension 400 mg BID with a high-fat meal. In this pooled analysis, the mean QT_c (Fridericia) interval change was -5 msec following administration of the recommended clinical dose. A decrease in the QT_c (F) interval (- 3 msec) was also observed in a small number of subjects (n=16) administered placebo. No subject administered posaconazole oral suspension had a QT_c (F) interval of $\geq$ 500 msec or an increase $\geq$ 60 msec in their QT_c (F) interval from baseline.

5.3 PRECLINICAL SAFETY DATA

Pre-clinical safety
In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2-8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioural or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). The clinical significance of this finding is unknown; therefore, the use of posaconazole concentrated injection in patients under 18 years of age is not recommended (see **Section 4.2 Dose and Method of Administration**).

Genotoxicity

Posaconazole has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, mammalian mutation and human lymphocyte chromosomal aberration) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, posaconazole did not cause genetic damage.

Carcinogenicity

Posaconazole administered by the oral route caused an increase in hepatocellular adenomas in mice at plasma exposure levels ~7-times higher than anticipated in humans at the maximum recommended clinical dose. This finding is considered to have occurred secondary to liver toxicity in the species, and mice are known to be particularly susceptible to this neoplastic change.

Rats treated with posaconazole administered by the oral route at exposure levels ≥ 2.4-times that of humans developed adrenal cortical cell adenomas and/or carcinomas and phaeochromocytomas. The cortical tumours are consistent with endocrinological disruption following chronic impairment of adrenal steroidogenesis. The increase in phaeochromocytomas is considered to be a rat-specific phenomenon that follows changes in calcium homeostasis. Altered calcium homeostasis has not been observed in humans receiving posaconazole. The results of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial of NOXAFIL concentrated injection contains the following inactive ingredients: sulfobutyl betadex sodium (SBECD), disodium edetate, hydrochloric acid, sodium hydroxide and Water for Injections.

6.2 INCOMPATIBILITIES

NOXAFIL concentrated injection must not be diluted with Lactated Ringer's solution, 5% dextrose with Lactated Ringer's solution, 4.2% sodium bicarbonate.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C - 8°C (Refrigerate. Do not freeze).

6.5 NATURE AND CONTENTS OF CONTAINER

NOXAFIL concentrated injection is available in a Type I glass vial closed with bromobutyl rubber stopper and aluminium seal containing 16.7 mL of solution (18 mg of posaconazole per mL).

NOXAFIL Concentrated Injection: AUST R 218702

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

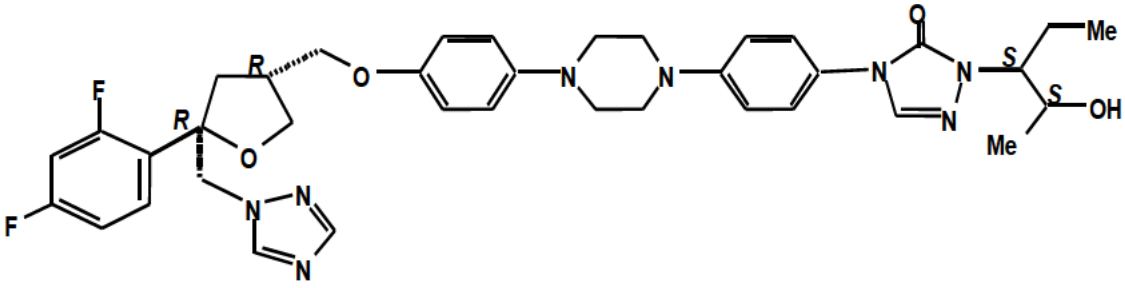
6.7 PHYSICOCHEMICAL PROPERTIES

Posaconazole is a broad spectrum triazole antifungal compound with a molecular formula of $C_{37}H_{42}F_2N_8O_4$ yielding a molecular weight of 700.8.

The chemical structure, which possesses four chiral centres, two R and two S, and chemical name are illustrated below:

Chemical structure

SCH 56592 (Posaconazole)



CAS INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydropropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl).

IUPAC NAME: 4-4-[4-(4-{(3R, 5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one.

CAS number
The CAS Registry Number is 171228-49-2.

7 MEDICINE SCHEDULE (POISONS STANDARD)

All states and ACT – Schedule 4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27 January 2015

10 DATE OF REVISION

03 Oct 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2 Dose and method of administration	Update to "Method of administration" as per CCDS-MK5592-IV-122015: - revision of administration instructions to include accommodation of a larger diluent bag size and a final concentration range - removal of recommendation text for use of in-line filter
4.7 Effects on ability to drive and use machines	Included relevant statement from Noxafil SmPC
All sections	PI reformat

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