ザルティア錠 5 mg
ザルティア錠 2.5 mg

日本イーライリリー株式会社

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1.5　起原又は発見の経緯及び開発の経緯

日本イーライリリー株式会社

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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 はじめに

前立腺肥大症に伴う排尿障害は、加齢に伴い増加する、高齢男性によく認められる疾患の一つであり、日常生活に支障をきたすことによりクオリティ・オブ・ライフ（QOL）を低下させる（McVary 2006、前立腺肥大症診療ガイドライン 2011）。前立腺肥大症は前立腺の良性疾患であり、組織学的には 60 歳男性の 50%以上に、85 歳まででは約 90%に認められ（Berry et al. 1984）、その約 1/4 に臨床症状が出現する（Oesterling 1991）。厚生労働省の調査報告によると、日本における前立腺肥大症の総受診患者数は 1998 年で 59.0 万人、2004 年で 98.4 万人、2010 年で 133.0 万人と増加を認めている（国民生活基礎調査、http://www.e-stat.go.jp/SG1/estat/NewList.do?tid=000001031016）。さらに、前立腺集団検診データから算出した治療を要する前立腺肥大症の患者数は 1995 年で 150 万人、2010 年で 198 万人であり、2030 年には 219 万人になると言われている（Terai et al. 2000）。

前立腺肥大症に伴う症状は、大きく蓄尿症状（昼間頻尿、尿意切迫感及び夜間頻尿）と排尿症状（開始時のいきみ、尿線細小、尿線途絶及び残尿感）に分けられ、前立腺肥大症に伴う排尿障害と呼ばれている（本間ら 2003）。

前立腺肥大症診療ガイドライン（2011 年版）によると、前立腺肥大症に伴う排尿障害に対する推奨治療方法は、1）経過観察、2）薬物療法［αアドレナリン受容体遮断剤（α遮断剤*）、5α還元酵素阻害剤（5-ARI）及びその他の薬物］、3）低侵襲治療、4）手術である。同ガイドラインでは、国内で承認されている薬剤の中で、α遮断剤及び 5-ARI は前立腺肥大症に伴う排尿障害患者への使用が強く推奨されている。また、α遮断剤（タムスロシンやシロドシンなど）、5-ARI（デュタステリド）又はその他の薬剤（アリルエストレノール、エビプロスタット、パラプロストなど）による複数回の薬物療法で十分な改善が認められない患者には、低侵襲治療及び手術が適しているとされている。手術適応については、明確な基準としては示されていないが、内服治療では効果が不十分と想定される場合や患者が手術を希望する場合などが挙げられている。

α遮断剤や 5-ARI などは下部尿路症状の軽減における有効性が証明されている一方、血圧低下に関する事象（浮動性めまいを含む）及び性機能障害に関連する事象（逆行性射精、リビドー減退及び勃起不全を含む）（前立腺肥大症診療ガイドライン 2011、ハルナール D 錠添付文書 2013 年 1 月、ユリーフ錠添付文書 2009 年 6 月、アボルブカプセル添付文書 2012 年 9 月）など、これらの薬物療法で認められる副作用は患者の QOL に影響を及ぼす可能性があり、治療開始前に考慮すべきである。したがって、前立腺肥大症に伴う排尿障害の治療の選択肢を広げる上で、既存の治療薬とは別の作用機序で、従来とは異なる安全性プロファイルを有する薬剤が求められている。

* 以下、特に断りがない限り、日本における治療の場合ではα_1遮断剤のことを指す。

1.5.2 起原又は発見の経緯

LY450190（タダラフィル）は生体内でサイクリックグアノシン 1 リン酸（cGMP）の分解を行っているホスホジエステラーゼ・タイプ 5（PDE5）の強力な選択的阻害剤であり、内因性一酸化窒素（NO）による cGMP レベルの上昇を増強させる。

タダラフィルの開発はグラクソ・ウェルカム社が着手し、海外においてはアイコス社、続いてイーライリリー・アンド・カンパニーとアイコス社の合弁会社であるリリー・アイコス社が勃起不全治療剤としての開発を行った（リリー・アイコス社はその後イーライリリー・アンド・カンパニーに統合された）。日本国内については日本イーライリリー株式会社が開発を行い、2007 年 7 月 31 日に承認を取得した（販売名：シアリス錠 5 mg、10 mg、20 mg）。その後、肺動脈性肺高血圧症の治療剤としての開発も行い、海外においては当初はリリー・アイコス社が開発を行っていたが、イーライリリー・アンド・カンパニーへの統合以降はイーライリリー・アンド・カンパニーが開発を行った。日本国内については日本イーライリリー株式会社が開発を行い、2009 年 10 月 16 日に承認を取得した（販売名：アドシルカ錠 20 mg）。2012 年 10 月 15 日現在、タダラフィルは勃起不全治療剤又は肺動脈性肺高血圧症治療剤として日本を含め 124 ヵ国で承認され、114 ヵ国で販売されている。

PDE5 はヒト下部尿路組織においても高レベルで発現しており、前立腺や膀胱、その周辺血管の平滑筋においても、陰茎組織や肺動脈での作用と同様に、タダラフィルによる PDE5 阻害により cGMP 濃度が上昇する。cGMP 濃度上昇により血管が弛緩することで、血流及び酸素供給が増加し、下部尿路組織での知覚神経出力への影響と相まって前立腺肥大症に伴う排尿障害の症状が緩和されると推測される。また、前立腺や膀胱の平滑筋に対する弛緩作用が、膀胱機能を低下させることなく、これらの作用を補完している可能性がある（Dmochowski et al. 2010）。これらのことからタダラフィルは新たな作用機序を持つ前立腺肥大症に伴う排尿障害の治療薬として期待される。

前立腺肥大症に伴う排尿障害に対する治療薬として開発したザルティア錠（以下、本剤）の開発の経緯を図 1.5-1 に示し、以下にその概略を記載する。

1.5.2.1 製剤開発の経緯

1.5.2.1.1 原薬

本剤 2.5 mg 及び 5 mg の有効成分は、既承認医薬品であるシアリス錠及びアドシルカ錠の有効成分と同一である。

1.5.2.1.2 製剤

本剤 5 mg は、勃起不全治療剤として既に承認されているシアリス錠との識別を可能にするため、シアリス錠 5 mg のフィルムコーティング剤の処方と刻印のみを変更し、既承認製剤と色調の異なる錠剤として開発された。本剤 5 mg のフィルムコーティング剤の色は白色で、その処方はシアリス錠 5 mg のフィルムコーティング剤から[redacted]可能な[redacted]を除いたものである。この処方変更は「後発医薬品の生物学的同等性試験ガイドライン等の一部改正について」（平成 24 年 2 月 29 日薬食審査発 0229 第 10 号）

の別紙 3「経口固形製剤の処方変更の生物学的同等性試験ガイドライン」における A 水準の変更に該当する。そこで、このガイドラインに従って、規格及び試験方法の溶出試験条件下で本剤 5 mg 及びシアリス錠 5 mg の溶出挙動を比較したところ、両製剤の溶出挙動の同等性が確認された。

本剤 2.5 mg は既承認医薬品と含量が異なる製剤であり、外国で市販されているシアリス錠 2.5 mg と素錠及びフィルムコーティング層が同一で、刻印のみが異なっている。本剤 2.5 mg のフィルムコーティング剤の色は黄色で、[redacted]及び[redacted]を含む。

タダラフィルを有効成分とする 2.5 mg 錠、5 mg 錠及び 10 mg 錠*間の生物学的同等性については H6D-EW-LVBX 試験（LVBX 試験）で確認されている（第 2.7.1 項参照）。

＊10 mg 錠は本承認申請の対象外である。

1.5.2.2 非臨床試験の経緯

勃起不全を効能・効果（10 及び 20 mg 必要時投与）とする開発時に、一連の薬理試験、薬物動態試験及び毒性試験を広範に実施した［シアリス錠医薬品製造販売承認時 CTD（以下、シアリス錠 CTD）参照］。これらの試験成績は肺動脈性肺高血圧症を効能・効果（40 mg 連日投与）とする開発時にも利用した。反復投与毒性試験は連日投与で実施しており、前立腺肥大症に伴う排尿障害を対象とした推奨用法用量（5 mg 連日投与）の安全性を評価するために必要な試験成績は得られていると判断し、新たな毒性試験は実施しなかった。前立腺肥大症に伴う排尿障害に対するタダラフィルの作用機序に関連する既存の文献データを補完する目的で、高血圧自然発症ラットを用いた試験及びヒト組織標本を用いた *in vitro* 試験を実施した（AMS42、第 4.2.1.1.1 項）。これらの試験で得られた成績は、NO/cGMP を介した血管弛緩による下部尿路組織への血流増加がタダラフィルの前立腺肥大症に伴う排尿障害に対する効果に寄与し、更に、前立腺や膀胱の平滑筋に対する弛緩作用や膀胱求心性神経活動の抑制が血管に対する作用を補完するとする既存の文献報告（総説、Andersson et al. 2011）と一致するものであった。また、タダラフィルの排尿機能改善作用を評価する目的で、正常ラットを用いた試験（[redacted]0771、第 4.2.1.1.2 項）及び排尿機能障害ラットモデルを用いた試験（[redacted]0231、第 4.2.1.1.3 項）を実施したが、これらの 2 試験では有意な作用は認められなかった。前立腺肥大症の病態生理学的な特徴に類似性を示す動物モデルは存在し、PDE5 阻害作用による影響も報告されているが、前立腺肥大症に伴う排尿障害を完全に反映する動物モデルは確立されておらず、また、タダラフィルの前立腺肥大症に伴う排尿障害に対する治療効果は臨床試験で示されていることから、別の動物モデルを用いた更なる検討は実施しなかった。

1.5.2.3 臨床開発の経緯

1.5.2.3.1 外国における臨床開発

本剤の欧米における前立腺肥大症に伴う排尿障害に対する開発は[redacted]年から開始し、最初の臨床試験として Proof-of-Concept 試験と位置づけた前期第 II 相無作為化二重盲検プラセボ対照並行群間比較試験［H6D-MC-LVGC 試験（LVGC 試験）、第 5.3.5.1.10 項］

を実施した。LVGC 試験の結果より本剤の前立腺肥大症に伴う排尿障害に対する有効性及び安全性が示唆されたため、米国及び欧州において第 II/III 相無作為化二重盲検プラセボ対照用量反応性試験［H6D-MC-LVHG 試験（LVHG 試験_DB 期間）、第 5.3.5.1.4 項］を実施した。LVHG 試験_DB 期間では LVGC 試験で認められた有効性及び安全性が確認された。LVHG 試験_DB 期間において本剤の前立腺肥大症に伴う排尿障害を有する被験者における用量反応関係が示され、タダラフィル 5 mg 1 日 1 回投与で好ましいリスク・ベネフィットプロファイルが認められた。本試験の有効性及び安全性の結果を基に、[redacted]、第 III 相試験で検証すべき推奨用量としてタダラフィル 5 mg 1 日 1 回投与を選択した。

その後、第 III 相プラセボ対照試験である H6D-MC-LVHJ 試験（LVHJ 試験、第 5.3.5.1.5 項）、H6D-MC-LVHR 試験（LVHR 試験、第 5.3.5.1.6 項）及び H6D-MC-LVID 試験（LVID 試験、第 5.3.5.1.7 項）によってタダラフィル 5 mg 1 日 1 回投与の有効性と安全性を検証した。また、LVHG 試験_DB 期間の長期継続試験である LVHG 試験の非盲検継続期間（LVHG 試験_OLE 期間、第 5.3.5.2.2 項）において、タダラフィル 5 mg を 1 日 1 回長期投与（54 週間）した際の安全性及び有効性の確認を行った。

さらに、タダラフィル 1 日 1 回投与の尿流動態における影響を評価する尿流動態試験［H6D-MC-LVHK 試験（LVHK 試験）、第 5.3.5.1.11 項］及びα遮断剤及び本剤を併用した際の血行動態上の副作用を検討する臨床試験［H6D-MC-LVHS 試験（LVHS 試験）、第 5.3.5.1.8 項］、韓国におけるプラセボ対照パイロット試験［H6D-MC-LVHT 試験、（LVHT 試験）、第 5.3.5.1.12 項］を実施した。また、前立腺肥大症に伴う排尿障害の適応症追加のための試験として臨床薬理試験［H6D-EW-LVHN 試験（LVHN 試験）、第 5.3.3.3.2 項］を実施した。LVHN 試験では前立腺肥大症に伴う排尿障害を有する非高齢患者及び高齢患者におけるタダラフィル 20 mg 1 日 1 回投与時の薬物動態及び血行動態について評価した。

これらの試験結果より、外国において本剤の前立腺肥大症に伴う排尿障害を有する患者に対するタダラフィル 5 mg 1 日 1 回投与時の有効性及び安全性並びに忍容性が確認できたため、米国では 2010 年 12 月 6 日に「前立腺肥大症の徴候及び症状の治療」及び「勃起不全並びに前立腺肥大症の徴候及び症状の治療」を適応として承認申請を行い、2011 年 10 月 6 日に承認を取得した。また、LVID 試験終了後、EU において「勃起不全の併発患者を含む成人男性における前立腺肥大症の徴候及び症状の治療」を適応として 2011 年 9 月 7 日に承認申請を行い、「成人男性における前立腺肥大症の徴候及び症状の治療」を適応として 2012 年 10 月 24 日に承認を取得した（第 1.6 項参照）。

これらに加え、前立腺肥大症に伴う排尿障害及び前立腺腫大を有する患者におけるタダラフィル 5 mg（対照薬：プラセボ）とフィナステリド 5 mg を 1 日 1 回併用投与時の有効性及び安全性を評価した H6D-CR-LVIW 試験（LVIW 試験、第 5.3.5.1.9 項）、前立腺肥大症に伴う排尿障害を対象として前立腺の血流量及び灌流パラメータ（前立腺移行領域における動脈血流抵抗指数など）を評価した H6D-MC-LVIR 試験（LVIR 試験）が最近完了している。なお、LVIR 試験の結果は、[redacted]年[redacted]月以降にデータが得られたため、本申請のデータパッケージには含めていない。

1.5.2.3.2 日本における前立腺肥大症に伴う排尿障害の治療薬としての臨床開発

本剤の前立腺肥大症に伴う排尿障害に対する臨床開発を計画した当時、前立腺肥大症に伴う排尿障害における薬剤として国内で承認されていた薬剤は、α遮断剤及び抗男性ホルモン薬などであった。これらの治療薬は臨床的な有効性が示されているものの、α遮断剤の服用時には起立性低血圧やめまいの副作用、術中虹彩緊張低下症候群のリスクが報告されていた。また、射精障害やリビドー減退などの性機能に関連した副作用（Djavan et al. 2004、Hellstrom et al. 2009）は両薬剤に共通して認められ、患者のQOLに影響を及ぼしている可能性があった。

したがって、既存の治療薬とは異なる作用機序を持ち、これらの副作用やリスクの少ない新規の治療薬を開発することは、前立腺肥大症に伴う排尿障害を有する患者の治療選択肢を広げるという点において大きな意義があると考え、本剤の前立腺肥大症に伴う排尿障害に対する開発を国内で進めることとした。

1.5.2.3.2.1 医薬品後期第Ⅱ相試験開始前相談 [redacted]年[redacted]月[redacted]日、[redacted]

本剤の前立腺肥大症に伴う排尿障害に対する開発を国内で進めるに当たり、[redacted]年[redacted]月に治験相談を実施した。本相談では、[redacted]について相談し、以下の見解を得た。

- [redacted]と考える。
- [redacted]考える。[redacted]と考える。
- [redacted]を勧める。[redacted]と考える。
- [redacted]と考える。
- [redacted]と考える。

これらの見解に基づき、国内における開発のための臨床試験として、用量反応性試験［H6D-JE-LVIA 試験（LVIA 試験_DB 期間）：継続投与による長期投与（LVIA 試験_OLE 期間）、二重盲検（DB）期間における日本人患者の薬物動態の検討を含む、第5.3.5.1.1 項及び第 5.3.5.2.1 項］及び検証試験［H6D-MC-LVHB 試験（LVHB 試験）：臨床的位置づけを検討するためのタムスロシン群を含む、日本、韓国及び台湾が参加する国際共同試験、第 5.3.5.1.2 項］の 2 試験を実施することとした。また、いずれの試験においても、タダラフィル2用量群（2.5 及び 5 mg）を含めた。

1.5.2.3.2.2　用量反応性試験（LVIA 試験_DB 期間）

LVIA 試験_DB 期間は、前立腺肥大症に伴う排尿障害を有する 45 歳以上の日本人患者を対象に行った。試験デザインは、プラセボ対照、無作為化、二重盲検並行群間試験であった。被験者は、タダラフィル 2.5 mg 群、5 mg 群又はプラセボ群に 1：1：1 の割合で無作為に割り付けられ、12 週間投与を受けた。

LVIA 試験_DB 期間では、主要評価項目である IPSS トータルスコアのベースラインからの変化量において、タダラフィル 2.5 mg 群及び 5 mg 群とプラセボ群の間に統計学的有意差は認められなかったものの、用量依存的な改善傾向が認められた。副次的評価項目である IPSS QOL スコア及び IPSS 排尿症状スコアにおいて、タダラフィル 5 mg 群は、プラセボ群との間に統計学的有意差を示した。タダラフィル 5 mg 群において Q_{max} はベースラインから増加したが、その変化量は小さく、プラセボ群と比較して統計学的な有意差は認められなかった。また、タダラフィルの安全性に関して特記すべき新たな所見は認められなかった。

1.5.2.3.2.3　長期継続投与試験（LVIA 試験_OLE 期間）

LVIA 試験_DB 期間を終了し、タダラフィル 5 mg を 42 週にわたって投与する非盲検継続期間（LVIA 試験_OLE 期間：合計 54 週）に移行した被験者を対象に、タダラフィルの長期投与における安全性及び有効性を評価した。LVIA 試験_OLE 期間における安全性プロファイルは LVIA 試験_DB 期間で認められたものと類似しており、長期投与における新たな安全性の問題は認められなかった。また、様々な評価項目において有効性が、LVIA 試験_OLE 期間終了時（54 週目）まで維持されることが確認された。さらに、Q_{max} は LVIA 試験_OLE 期間において、増加する傾向を示した。

1.5.2.3.2.4　医薬品後期第Ⅱ相試験終了後相談 [redacted]年[redacted]月[redacted]日、[redacted]

LVIA 試験_DB 期間において、主要評価項目である IPSS トータルスコアでタダラフィル 2.5 mg 群及び 5 mg 群でプラセボ群との間に統計学的な有意差が認められなかったことから、[redacted]、[redacted]年[redacted]月に治験相談を実施した。当該相談では、[redacted]について相談し、以下の見解を得た。

- [redacted]と考える。
- [redacted]と考える。
- [redacted]と考える。
- [redacted]と考える。

これらの見解に基づき、[redacted]試験を完了した。

1.5.2.3.2.5 検証試験（LVHB 試験）

LVHB 試験は、前立腺肥大症に伴う排尿障害を有する 45 歳以上のアジア人患者（日本、韓国及び台湾）を対象に行った。試験デザインはプラセボ対照、無作為化、二重盲検並行群間比較試験であった。被験者は、タダラフィル 2.5 mg 群、5 mg 群、タムスロシン 0.2 mg 群又はプラセボ群に 1：1：1：1 の割合で無作為に割り付けられ、12 週間投与を受けた。

LVHB 試験において、タダラフィル 5 mg 1 日 1 回投与ではプラセボに比べ、12 週間後の IPSS トータルスコア、IPSS 排尿症状スコア及び IPSS 蓄尿症状スコア、IPSS QOL スコアにおいて統計学的に有意な改善が認められた。タダラフィル 5 mg 群において Q_{max} はベースラインから増加したが、その変化量においてはプラセボ群との間に統計学的な有意差は認められなかった。また、タダラフィルの安全性に関して特記すべき新たな所見は認められなかった。

1.5.2.3.2.6 医薬品申請前相談 [redacted]年[redacted]月[redacted]日、[redacted]

国内で実施した LVIA 試験_DB 期間及び LVHB 試験並びに外国における臨床試験の試験結果を基に、[redacted]年[redacted]月に対面助言を行い、以下の助言を得た。

- [redacted]

この PMDA の見解に基づき、タダラフィル 5 mg のプラセボに対する有効性の検証を目的としたアジア人（日本及び韓国）を対象とした第 III 相試験［H6D-JE-LVJF 試験（LVJF 試験）、第 5.3.5.1.3 項］を追加することとした。LVIA 試験及び LVHB 試験の結果の考察を踏まえた変更点は以下のとおりであった。

1. タダラフィル 5 mg 群及びプラセボ群の 2 群比較
2. 単盲検プラセボ導入期間（4 週間）の IPSS トータルスコア変化量を割付因子に追加
3. 症例数設定における IPSS トータルスコア変化量のプラセボ群とタダラフィル 5 mg 群の群間差を 1.5 と想定

1.5.2.3.2.7 検証試験（LVJF 試験）

LVJF 試験は、前立腺肥大症に伴う排尿障害を有する 45 歳以上のアジア人男性（日本及び韓国）を対象に行った。試験デザインはプラセボ対照、無作為化、二重盲検並行群

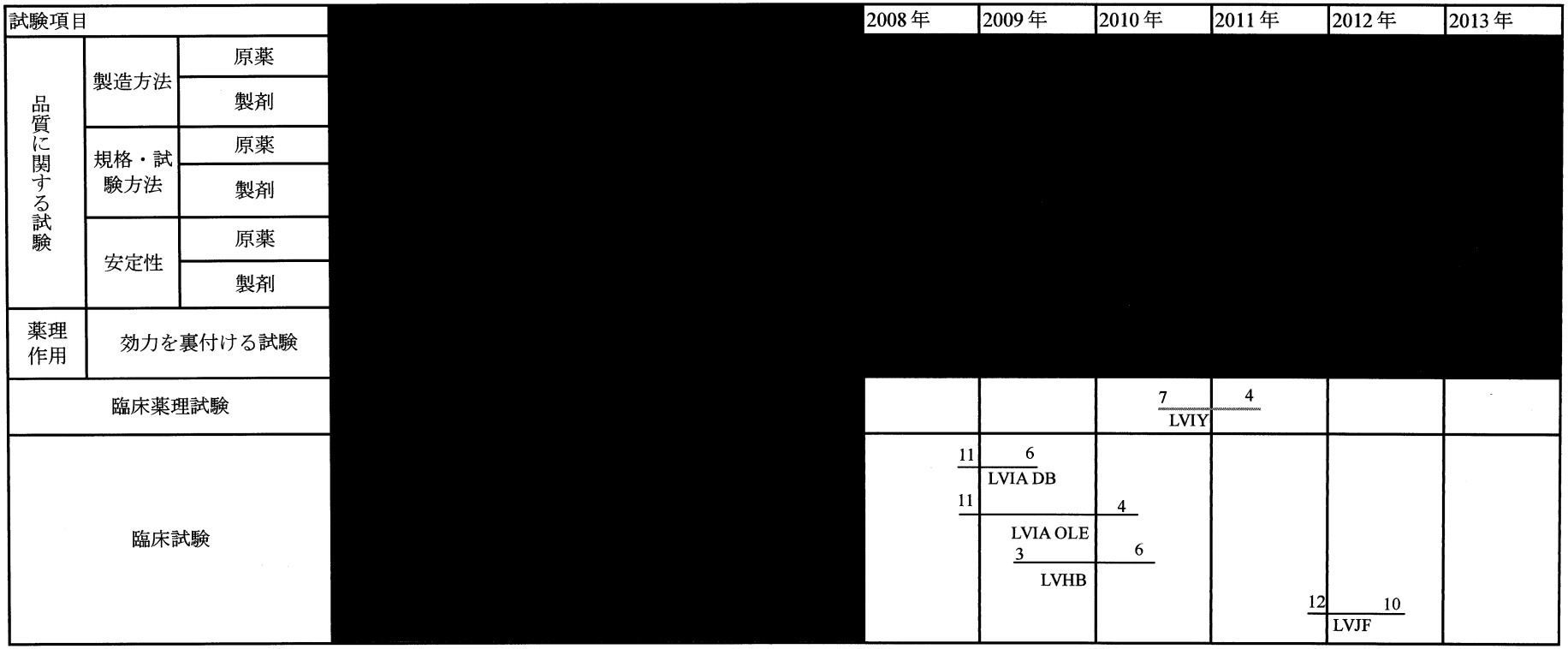
間比較試験であった。被験者は、タダラフィル 5 mg 群又はプラセボ群に 1：1 の割合で無作為に割り付けられ、12 週間投与を受けた。

LVJF 試験において、タダラフィル 5 mg 1 日 1 回投与ではプラセボに比べ、IPSS トータルスコア、IPSS 排尿症状スコア、IPSS 蓄尿症状スコア及び IPSS QOL スコアにおいて統計学的に有意な改善が認められた。また、タダラフィルの安全性に関して特記すべき新たな所見は認められなかった。

LVIA 試験（DB 期間及び OLE 期間）、LVHB 試験及び LVJF 試験に加え、前立腺肥大症に伴う排尿障害を有する日本人及び外国人を対象とした臨床薬理試験［H6D-MC-LVIY 試験（LVIY 試験）、第 5.3.3.3.1 項］も実施した。

これらの試験結果より、前立腺肥大症に伴う排尿障害を有する日本人患者に対するタダラフィル 5 mg 1 日 1 回投与時の有効性及び安全性並びに忍容性が確認できたため、「前立腺肥大症に伴う排尿障害」を効能・効果として今回製造承認申請を行うこととした。

図 1.5-1 ザルティア錠の開発の経緯図



——　国内におけるデータ

——　外国におけるデータ

ザルティア錠 5 mg
ザルティア錠 2.5 mg

1.6　外国における使用状況等に関する資料

日本イーライリリー株式会社

目次

1.6　外国における使用状況等に関する資料

LY450190（タダラフィル）は2012年12月現在、前立腺肥大症の治療に対して20の国と地域で、勃起不全及び前立腺肥大症の治療に対して9ヵ国で承認されている。販売名はすべての国においてCIALIS®である。外国における承認状況を表1.6-1に示した。

なお、2012年10月15日現在、タダラフィルは勃起不全治療剤又は肺動脈性肺高血圧症治療剤として日本を含め124ヵ国で承認され、114ヵ国で販売されている（国内販売名：勃起不全治療剤：シアリス錠、肺動脈性肺高血圧症治療剤：アドシルカ錠）。

表1.6-1 外国における承認状況（2012年12月調査）
（効能・効果：前立腺肥大症の治療又は勃起不全及び前立腺肥大症の治療）

	国名	申請日	承認日	前立腺肥大症の治療	勃起不全及び前立腺肥大症の治療
1	アルゼンチン	2012年1月31日	2012年3月1日	○	○
2	イスラエル	2011年12月5日	2012年6月21日	○	○
3	EU	2011年9月7日	2012年10月24日	○	-
4	エクアドル	2012年3月12日	2012年4月16日	○	-
5	カナダ	2011年8月2日	2012年7月3日	○	-
6	韓国	2011年11月2日	2012年5月21日	○	○
7	グアテマラ	2012年8月8日	2012年9月27日	○	-
8	コスタリカ	2012年1月25日	2012年6月13日	○	-
9	コロンビア	2012年1月26日	2012年7月12日	○	○
10	スペイン	2011年9月7日	2012年10月24日	○	-
11	タイ	2012年2月9日	2012年11月15日	○	○
12	台湾	2011年10月31日	2012年12月26日	○	-
13	チリ	2012年4月24日	2012年11月5日	○	-
14	トルコ	2012年9月21日	2012年11月21日	○	-
15	パナマ	2012年1月30日	2012年5月15日	○	-
16	ブラジル	2011年9月30日	2012年7月16日	-	○
17	米国	2010年12月6日	2011年10月6日	○	○
18	ボリビア	2012年7月27日	2012年12月18日	○	-
19	ホンジュラス	2012年2月8日	2012年5月15日	○	-
20	メキシコ	2011年9月9日	2011年11月15日	○	-
21	ルーマニア	2012年6月1日	2012年10月24日	-	○
22	ロシア	2011年10月28日	2012年5月31日	○	○

米国及びEUにおける添付文書の概略（剤型・含量、効能・効果、用法・用量）を表1.6-2に示し、米国の添付文書、EUの製品特性概要（Summary of Product Characteristics）及び企業中核データシート［Company Core Data Sheet（CCDS）］を添付した。

表 1.6-2 米国及び EU における剤型・含量、効能・効果、用法・用量
（2012 年 12 月調査）

	米国	EU
販売名	CIALIS®	CIALIS®
剤型・含量	錠剤 2.5 mg、5 mg、10 mg、20 mg	錠剤 2.5 mg、5 mg*、10 mg、20 mg *5 mg 錠のみ前立腺肥大症の徴候及び症状の治療に対して承認されている。
効能・効果	**勃起不全** CIALIS の適応症は勃起不全の治療である。 **前立腺肥大症** CIALIS の適応症は前立腺肥大症の徴候及び症状の治療である。 **勃起不全及び前立腺肥大症** CIALIS の適応症は勃起不全並びに前立腺肥大症の徴候及び症状の治療である。（勃起不全/前立腺肥大症）	成人男性における勃起不全の治療。 タダラフィル が勃起不全治療の効果を発現するには、性的刺激が必要である。 成人男性における前立腺肥大症の徴候及び症状の治療。 女性に対する適応はない。
用法・用量	**CIALIS 錠は割らずに服用すること。** **勃起不全に対する CIALIS の必要時投与** ・必要時投与における大部分の患者の推奨開始用量は 10 mg であり、予定される性行為の前に服用する。 ・個々の効果及び忍容性に応じて 20 mg まで増量又は 5 mg まで減量することができる。大部分の患者の推奨投与回数は最大 1 日 1 回である。 ・CIALIS はプラセボと比較し、投与後 36 時間まで勃起機能を改善することが示された。したがって、患者に CIALIS の至適用法を説明する際には、この点を考慮に入れる必要がある。 **勃起不全に対する CIALIS の 1 日 1 回投与** ・CIALIS 1 日 1 回投与における推奨開始用量は 2.5 mg であり、性行為のタイミングに関わらず毎日ほぼ同じ時刻に投与すること。 ・CIALIS の 1 日 1 回投与では、個々の効果及び忍容性に応じて 5 mg まで増量してもよい。 **前立腺肥大症に対する CIALIS の 1 日 1 回投与** CIALIS 1 日 1 回投与における推奨用量は 5 mg であり毎日ほぼ同じ時刻に投与すること。 **勃起不全/前立腺肥大症に対する CIALIS の 1 日 1 回投与** CIALIS 1 日 1 回投与における推奨用量は 5 mg であり、性行為のタイミン	**成人男性における勃起不全** 一般に、推奨用量は 10 mg であり、食事の有無にかかわらず、予定される性行為の前に投与する。 タダラフィル 10 mg で十分な効果が得られない場合には、20 mg を服用することができる。 性行為の 30 分以上前に服用する。 最大投与回数は 1 日 1 回である。 タダラフィル 10 mg 及び 20 mg は性行為の前に使用するものであり、継続的に連日投与することは推奨されない。 CIALIS を頻繁に（例えば、週に 2 回以上）投与することが予測される患者においては、患者の選択及び医師の判断に基づいて、最低用量の CIALIS 1 日 1 回投与が適切かもしれない。 これらの患者においては、5 mg を 1 日 1 回ほぼ同じ時刻に投与すること。個々の忍容性に応じて 2.5 mg 1 日 1 回投与まで減量してもよい。 1 日 1 回投与による治療を継続して行う場合は定期的に再評価すること。 **成人男性における前立腺肥大症** 推奨用量は 5 mg であり、毎日ほぼ同じ時刻に食事の有無にかかわらず投与すること。前立腺肥大症及び勃起不全の両方に対して治療を行う成人男性においては、推奨用量は 5 mg であり、毎日ほぼ同じ時刻に投与すること。 タダラフィル 2.5 mg は前立腺肥大症の治療に効果が認められていないため、前

	米国	EU
	グに関わらず毎日ほぼ同じ時刻に投与すること。 **食後の使用** CIALIS は食事の有無にかかわらず投与することができる。 **特別な集団における使用** 腎障害 *CIALIS の必要時投与* ・クレアチニン・クリアランス 30～50 mL/分：開始用量は 5 mg で 1 日 1 回を超えないことが推奨される。最高用量は 10 mg で 48 時間に 1 回を超えないこととする。 ・クレアチニン・クリアランス<30 mL/分又は血液透析中の患者：最高用量は 5 mg で 72 時間に 1 回を超えないこととする。 *CIALIS の 1 日 1 回投与* 勃起不全 ・クレアチニン・クリアランス<30 mL/分又は血液透析中の患者：CIALIS の 1 日 1 回投与は推奨されない。 前立腺肥大症及び勃起不全/前立腺肥大症 ・クレアチニン・クリアランス 30～50 mL/分：開始用量は 2.5 mg が推奨される。個々の患者の状態に応じて 5 mg への増量を検討してもよい。 ・クレアチニン・クリアランス<30 mL/分又は血液透析中の患者：CIALIS の 1 日 1 回投与は推奨されない。 肝障害 *CIALIS の必要時投与* ・軽度又は中等度（Child-Pugh Class A 又は B）：投与量は 1 日 1 回 10 mg を超えてはならない。CIALIS の 1 日 1 回投与は肝障害患者において広範に評価されていないため注意すべきである。 ・重度（Child-Pugh Class C）：CIALIS の使用は推奨されない。 *CIALIS の 1 日 1 回投与* ・軽度又は中等度（Child-Pugh Class A 又は B）：CIALIS の 1 日 1 回投与は肝障害患者において広範に評価されていない。したがって、これらの患者に CIALIS の 1 日 1 回投与を処方する際は注意すべきである。 ・重度（Child-Pugh Class C）：CIALIS の使用は推奨されない。 **併用薬** 硝酸剤 硝酸剤との併用投与は剤形の種類を	立腺肥大症の治療においてタダラフィル 5 mg に忍容性のない患者においては、別の治療を検討すべきである。 **特別な集団** 高齢男性 高齢患者に対する用量調節の必要はない。 腎障害のある男性 軽度又は中等度の腎障害患者に対する用量調節の必要はない。重度の腎障害患者における必要時投与の推奨最高用量は 10 mg である。 勃起不全又は前立腺肥大症のどちらの治療においても、重度の腎障害患者に対するタダラフィル 2.5 mg 又は 5 mg の 1 日 1 回投与は推奨されない。 肝障害を有する男性 勃起不全治療における CIALIS の必要時投与の推奨用量は 10 mg であり、食事の有無にかかわらず、予定される性行為の前に服用する。重度（Child-Pugh Class C）の肝障害患者における CIALIS の安全性に関する臨床データは少ない。したがって、重度の肝障害患者に CIALIS を処方する場合には、処方する医師が注意深く個々のベネフィット・リスク評価を行う必要がある。肝障害患者に対して 10 mg を超える用量のタダラフィルを投与したデータは得られていない。 肝障害患者における CIALIS の 1 日 1 回投与は勃起不全の治療及び前立腺肥大症の治療のどちらにおいても評価されていない。したがって、肝障害患者に CIALIS を処方する場合には、処方する医師が注意深く個々のベネフィット・リスク評価を行う必要がある。 糖尿病のある男性 糖尿病患者に対する用量調節の必要はない。 小児 勃起不全治療に関する CIALIS 投与は小児には関係しない。 **投与方法** CIALIS は経口投与のための 2.5、5、10 及び 20 mg のフィルムコート錠である。

	米国	EU
	問わず禁忌である。 α遮断剤 *勃起不全*—CIALIS をα遮断剤と併用する場合には、患者が CIALIS 投与開始前にα遮断剤の治療で安定した状態にあること。また、最低推奨用量から CIALIS 投与を開始すべきである。 *前立腺肥大症*—前立腺肥大症の治療では CIALIS とα遮断剤の併用は推奨されない。 CYP3A4 阻害 *CIALIS の必要時投与*—ケトコナゾールやリトナビルのように強力な CYP3A4 阻害剤を服用中の患者に対する CIALIS の推奨最高用量は 10 mg とし、72 時間に 1 回を超えて投与しないこと。 *CIALIS の 1 日 1 回投与*—ケトコナゾールやリトナビルのように強力な CYP3A4 阻害剤を服用中の患者に対する CIALIS の推奨最高用量は 2.5 mg である。	

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

CIALIS (tadalafil) tablets, for oral use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Indications and Usage, Limitation of Use (1.4) 10/2013

Dosage and Administration, CIALIS for Once Daily Use for Benign Prostatic Hyperplasia (2.3) 10/2013

----------INDICATIONS AND USAGE----------

CIALIS® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of:

- erectile dysfunction (ED) (1.1)
- the signs and symptoms of benign prostatic hyperplasia (BPH) (1.2)
- ED and the signs and symptoms of BPH (ED/BPH) (1.3)

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks (1.4).

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

- *CIALIS for use as needed:*
- ED: Starting dose: 10 mg as needed prior to sexual activity. Increase to 20 mg or decrease to 5 mg based upon efficacy/tolerability. Improves erectile function compared to placebo up to 36 hours post dose. Not to be taken more than once per day (2.1).
- *CIALIS for once daily use:*
- ED: 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability (2.2).
- BPH: 5 mg, taken at approximately the same time every day (2.3)
- ED and BPH: 5 mg, taken at approximately the same time every day (2.3, 2.4)
- CIALIS may be taken without regard to food (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg (3).

----------CONTRAINDICATIONS----------

- Administration of CIALIS to patients using any form of organic nitrate is contraindicated. CIALIS was shown to potentiate the hypotensive effect of nitrates (4.1).
- History of known serious hypersensitivity reaction to CIALIS or ADCIRCA® (4.2).

----------WARNINGS AND PRECAUTIONS----------

- Patients should not use CIALIS if sex is inadvisable due to cardiovascular status (5.1).
- Use of CIALIS with alpha-blockers, antihypertensives or substantial amounts of alcohol (≥5 units) may lead to hypotension (5.6, 5.9).
- CIALIS is not recommended in combination with alpha-blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when CIALIS is used as a treatment for ED in men taking alpha-blockers. (2.7, 5.6, 7.1, 12.2)
- Patients should seek emergency treatment if an erection lasts >4 hours. Use CIALIS with caution in patients predisposed to priapism (5.3).
- Patients should stop CIALIS and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of Non Arteritic Ischemic Optic Neuropathy (NAION). Discuss increased risk of NAION in patients with history of NAION (5.4).
- Patients should stop CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5).
- Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms (5.14).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

- CIALIS can potentiate the hypotensive effects of nitrates, alpha-blockers, antihypertensives or alcohol (7.1).
- CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase CIALIS exposure (2.7, 5.10, 7.2) requiring dose adjustment:
  - CIALIS for use as needed: no more than 10 mg every 72 hours
  - CIALIS for once daily use: dose not to exceed 2.5 mg
- CYP3A4 inducers (e.g. rifampin) decrease CIALIS exposure (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (2.6, 5.8, 8.6):

- Mild or Moderate: Dosage adjustment may be needed.
- Severe: Use is not recommended.

Renal Impairment (2.6, 5.7, 8.7):

- Patients with creatinine clearance 30 to 50 mL/min: Dosage adjustment may be needed.
- Patients with creatinine clearance less than 30 mL/min or on hemodialysis: For use as needed: Dose should not exceed 5 mg every 72 hours. Once daily use is not recommended.

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

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Erectile Dysfunction

CIALIS® is indicated for the treatment of erectile dysfunction (ED).

1.2 Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

1.3 Erectile Dysfunction and Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

1.4 Limitation of Use

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of CIALIS decreases from 4 weeks until 26 weeks, and the incremental benefit of CIALIS beyond 26 weeks is unknown *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

Do not split CIALIS tablets; entire dose should be taken.

2.1 CIALIS for Use as Needed for Erectile Dysfunction

- The recommended starting dose of CIALIS for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.
- The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.
- CIALIS for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of CIALIS, this should be taken into consideration.

2.2 CIALIS for Once Daily Use for Erectile Dysfunction

- The recommended starting dose of CIALIS for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.
- The CIALIS dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

2.3 CIALIS for Once Daily Use for Benign Prostatic Hyperplasia

- The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day.
- When therapy for BPH is initiated with CIALIS and finasteride, the recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks.

2.4 CIALIS for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

2.5 Use with Food

CIALIS may be taken without regard to food.

2.6 Use in Specific Populations

Renal Impairment

CIALIS for Use as Needed

- Creatinine clearance 30 to 50 mL/min: A starting dose of 5 mg not more than once per day is recommended, and the maximum dose is 10 mg not more than once in every 48 hours.
- Creatinine clearance less than 30 mL/min or on hemodialysis: The maximum dose is 5 mg not more than once in every 72 hours *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

Erectile Dysfunction

- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia

- Creatinine clearance 30 to 50 mL/min: A starting dose of 2.5 mg is recommended. An increase to 5 mg may be considered based on individual response.
- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Hepatic Impairment

CIALIS for Use as Needed

- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10 mg once per day. The use of CIALIS once per day has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

- Mild or moderate (Child Pugh Class A or B): CIALIS for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

2.7 Concomitant Medications

Nitrates

Concomitant use of nitrates in any form is contraindicated *[see Contraindications (4.1)]*.

Alpha-Blockers

ED — When CIALIS is coadministered with an alpha-blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and CIALIS should be initiated at the lowest recommended dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

BPH — CIALIS is not recommended for use in combination with alpha-blockers for the treatment of BPH *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

CYP3A4 Inhibitors

CIALIS for Use as Needed — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of CIALIS is 10 mg, not to exceed once every 72 hours *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

CIALIS for Once Daily Use — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose is 2.5 mg *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow:
2.5 mg tablets debossed with "C 2 1/2"
5 mg tablets debossed with "C 5"
10 mg tablets debossed with "C 10"
20 mg tablets debossed with "C 20"

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of CIALIS to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates *[see Clinical Pharmacology (12.2)]*.

4.2 Hypersensitivity Reactions

CIALIS is contraindicated in patients with a known serious hypersensitivity to tadalafil (CIALIS or ADCIRCA®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

Evaluation of erectile dysfunction and BPH should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing CIALIS, it is important to note the following:

5.1 Cardiovascular

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including CIALIS, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention. *[see Contraindications (4.1) and Patient Counseling Information (17.1)]*.

Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for CIALIS, and therefore until further information is available, CIALIS is not recommended for the following groups of patients:

- myocardial infarction within the last 90 days
- unstable angina or angina occurring during sexual intercourse
- New York Heart Association Class 2 or greater heart failure in the last 6 months
- uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension
- stroke within the last 6 months.

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects *[see Clinical Pharmacology (12.2)]*. While this effect should not be of consequence in most patients, prior to prescribing CIALIS, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

5.2 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should be aware that CIALIS for once daily use provides continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, anti-hypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol *[see Drug Interactions (7.1, 7.2, 7.3)]*.

5.3 Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

CIALIS should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

5.4 Eye

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely

postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors *[see Adverse Reactions (6.2)]*.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

5.5 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

5.6 Alpha-blockers and Antihypertensives

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

ED

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other antihypertensive drugs.

[see Dosage and Administration (2.7) and Drug Interactions (7.1)].

BPH

- The efficacy of the coadministration of an alpha-blocker and CIALIS for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of CIALIS and alpha-blockers is not recommended for the treatment of BPH. *[see Dosage and Administration (2.7), Drug Interactions (7.1), and Clinical Pharmacology (12.2.)]*.
- Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting CIALIS for once daily use for the treatment of BPH.

5.7 Renal Impairment

CIALIS for Use as Needed

CIALIS should be limited to 5 mg not more than once in every 72 hours in patients with creatinine clearance less than 30 mL/min or end-stage renal disease on hemodialysis. The starting dose of CIALIS in patients with creatinine clearance 30 – 50 mL/min should be 5 mg not more than once per day, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. *[see Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

ED

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min *[see Use in Specific Populations (8.7)]*.

BPH and ED/BPH

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min. In patients with creatinine clearance 30 – 50 mL/min, start dosing at 2.5 mg once daily, and increase the dose to 5 mg once daily based upon individual response *[see Dosage and Administration (2.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.8 Hepatic Impairment

CIALIS for Use as Needed

In patients with mild or moderate hepatic impairment, the dose of CIALIS should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

CIALIS for once daily use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

5.9 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Clinical Pharmacology (12.2)]*.

5.10 Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

CIALIS is metabolized predominantly by CYP3A4 in the liver. The dose of CIALIS for use as needed should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole *[see Drug Interactions (7.2)]*. In patients taking potent inhibitors of CYP3A4 and CIALIS for once daily use, the maximum recommended dose is 2.5 mg *[see Dosage and Administration (2.7)]*.

5.11 Combination With Other PDE5 Inhibitors or Erectile Dysfunction Therapies

The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take CIALIS with other PDE5 inhibitors, including ADCIRCA.

5.12 Effects on Bleeding

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. CIALIS has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although CIALIS has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

5.13 Counseling Patients About Sexually Transmitted Diseases

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

5.14 Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH

Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Tadalafil was administered to over 9000 men during clinical trials worldwide. In trials of CIALIS for once daily use, a total of 1434, 905, and 115 were treated for at least 6 months, 1 year, and 2 years, respectively. For CIALIS for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

CIALIS for Use as Needed for ED

In eight primary placebo-controlled clinical studies of 12 weeks duration, mean age was 59 years (range 22 to 88) and the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo treated patients.

When taken as recommended in the placebo-controlled clinical trials, the following adverse reactions were reported (*see* Table 1) for CIALIS for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for CIALIS for Use as Needed for ED

Adverse Reaction	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%

Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing[a]	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

[a] The term flushing includes: facial flushing and flushing

CIALIS for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 or 24 weeks duration, mean age was 58 years (range 21 to 82) and the discontinuation rate due to adverse events in patients treated with tadalafil was 4.1%, compared to 2.8% in placebo-treated patients.

The following adverse reactions were reported (*see* Table 2) in clinical trials of 12 weeks duration:

Table 2: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in the Three Primary Placebo-Controlled Phase 3 Studies of 12 weeks Treatment Duration (Including a Study in Patients with Diabetes) for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=248)	Tadalafil 2.5 mg (N=196)	Tadalafil 5 mg (N=304)
Headache	5%	3%	6%
Dyspepsia	2%	4%	5%
Nasopharyngitis	4%	4%	3%
Back pain	1%	3%	3%
Upper respiratory tract infection	1%	3%	3%
Flushing	1%	1%	3%
Myalgia	1%	2%	2%
Cough	0%	4%	2%
Diarrhea	0%	1%	2%
Nasal congestion	0%	2%	2%
Pain in extremity	0%	1%	2%
Urinary tract infection	0%	2%	0%
Gastroesophageal reflux disease	0%	2%	1%
Abdominal pain	0%	2%	1%

The following adverse reactions were reported (*see* Table 3) over 24 weeks treatment duration in one placebo-controlled clinical study:

Table 3: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in One Placebo-Controlled Clinical Study of 24 Weeks Treatment Duration for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=94)	Tadalafil 2.5 mg (N=96)	Tadalafil 5 mg (N=97)
Nasopharyngitis	5%	6%	6%
Gastroenteritis	2%	3%	5%
Back pain	3%	5%	2%
Upper respiratory tract infection	0%	3%	4%
Dyspepsia	1%	4%	1%
Gastroesophageal reflux disease	0%	3%	2%
Myalgia	2%	4%	1%
Hypertension	0%	1%	3%
Nasal congestion	0%	0%	4%

CIALIS for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, two in patients with BPH and one in patients with ED and BPH, the mean age was 63 years (range 44 to 93) and the discontinuation rate due to adverse events in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to

discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. The following adverse reactions were reported (*see* Table 4).

Table 4: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with CIALIS for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration, including Two Studies for CIALIS for Once Daily Use for BPH and One Study for ED and BPH

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequent adverse reactions (<1%) reported in the controlled clinical trials of CIALIS for BPH or ED and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Tables 1 through 4. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g., codeine) was used. Overall, approximately 0.5% of all subjects treated with CIALIS for on demand use discontinued treatment as a consequence of back pain/myalgia. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Incidence rates for CIALIS for once daily use for ED, BPH and BPH/ED are described in Tables 2, 3 and 4. In studies of CIALIS for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across all studies with any CIALIS dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials of CIALIS for once daily use or use as needed. A causal relationship of these events to CIALIS is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a Whole — asthenia, face edema, fatigue, pain

Cardiovascular — angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia

Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage

Musculoskeletal — arthralgia, neck pain

Nervous — dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo

Renal and Urinary — renal impairment

Respiratory — dyspnea, epistaxis, pharyngitis

Skin and Appendages — pruritus, rash, sweating

Ophthalmologic — blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids

Otologic — sudden decrease or loss of hearing, tinnitus

Urogenital — erection increased, spontaneous penile erection

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CIALIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and Cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of CIALIS without sexual activity. Others were reported to have occurred hours to days after the use of CIALIS and sexual activity. It is not possible to determine whether these events are related directly to CIALIS, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

Body as a Whole — hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous — migraine, seizure and seizure recurrence, transient global amnesia

Ophthalmologic — visual field defect, retinal vein occlusion, retinal artery occlusion

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.4)]*.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including CIALIS. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of CIALIS, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions (5.5)]*.

Urogenital — priapism *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with CIALIS

Nitrates — Administration of CIALIS to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Dosage and Administration (2.7), Contraindications (4.1), and Clinical Pharmacology (12.2)]*.

Alpha-Blockers — Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), and Clinical Pharmacology (12.2)]*.

Antihypertensives — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*.

Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*.

7.2 Potential for Other Drugs to Affect CIALIS

[See Dosage and Administration (2.7) and Warnings and Precautions (5.10)].

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2 Antagonists (e.g. Nizatidine) — An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors — CIALIS is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

CYP3A4 (e.g., Ketoconazole) — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone *[see Dosage and Administration (2.7)]*.

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

HIV Protease inhibitor — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure *[see Dosage and Administration (2.7)]*.

Cytochrome P450 Inducers — Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

CYP3A4 (e.g., Rifampin) — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of CIALIS for once daily use; the magnitude of decreased efficacy is unknown.

7.3 Potential for CIALIS to Affect Other Drugs

Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates — CIALIS is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline) — Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g. Warfarin) — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 (e.g. Midazolam or Lovastatin) — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein *(e.g. Digoxin)* — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B — CIALIS (tadalafil) is not indicated for use in women. There are no adequate and well controlled studies of CIALIS use in pregnant women.

Risk Summary — Based on animal data, CIALIS is not predicted to increase the risk of adverse developmental abnormalities in humans.

Animal Data — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 10 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 16 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

In a rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 16 and 10 fold exposure multiples, respectively, of the human AUC for the MRHD of 20 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

8.3 Nursing Mothers

CIALIS is not indicated for use in women. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

8.4 Pediatric Use

CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

8.5 Geriatric Use

Of the total number of subjects in ED clinical studies of tadalafil, approximately 25 percent were 65 and over, while approximately 3 percent were 75 and over. Of the total number of subjects in BPH clinical studies of tadalafil (including the ED/BPH study), approximately 40 percent were over 65, while approximately 10 percent were 75 and over. In these clinical trials, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). Therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered. *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). *[see Dosage and Administration (2.6) and Warnings and Precautions (5.8)]*.

8.7 Renal Impairment

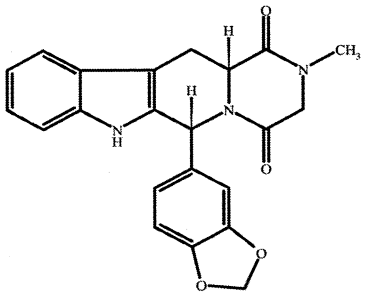
In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[see Dosage and Administration (2.6) and Warnings and Precautions (5.7)]*.

10 OVERDOSAGE

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

11 DESCRIPTION

CIALIS (tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as almond-shaped tablets for oral administration. Each tablet contains 2.5, 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). *In vitro*, tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

12.2 Pharmacodynamics

Effects on Blood Pressure

Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure When Administered with Nitrates

In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of CIALIS in patients taking any form of nitrates is contraindicated *[see Contraindications (4.1)]*.

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (*see* Figure 1).

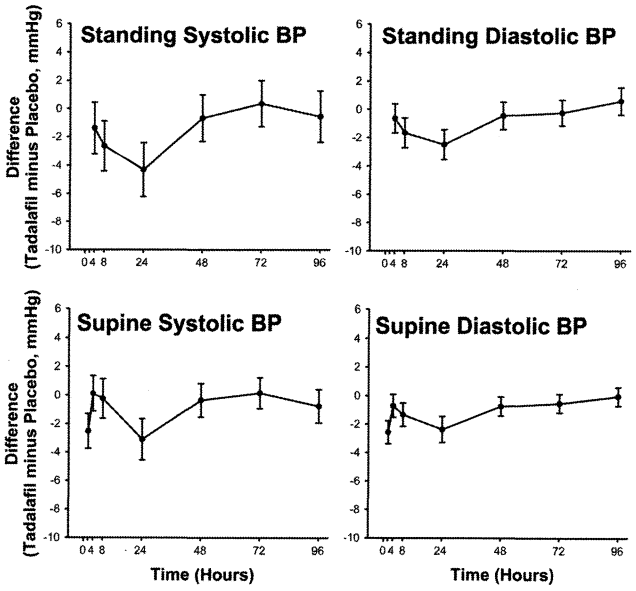


Figure 1: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, CIALIS administration with nitrates is contraindicated. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1)]*.

Effect on Blood Pressure When Administered With Alpha-Blockers

Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects *[see Dosage and Administration (2.7) and Warnings and Precautions (5.6)]*. In four studies, a single oral dose of tadalafil was administered to healthy male subjects taking daily (at least 7 days duration) an oral alpha-blocker. In two studies, a daily oral alpha-blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of tadalafil.

Doxazosin — Three clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha[1]-adrenergic blocker.

In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of seven days of doxazosin dosing (*see* Table 5 and Figure 2).

Table 5: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	3.6 (-1.5, 8.8)
Standing	9.8 (4.1, 15.5)

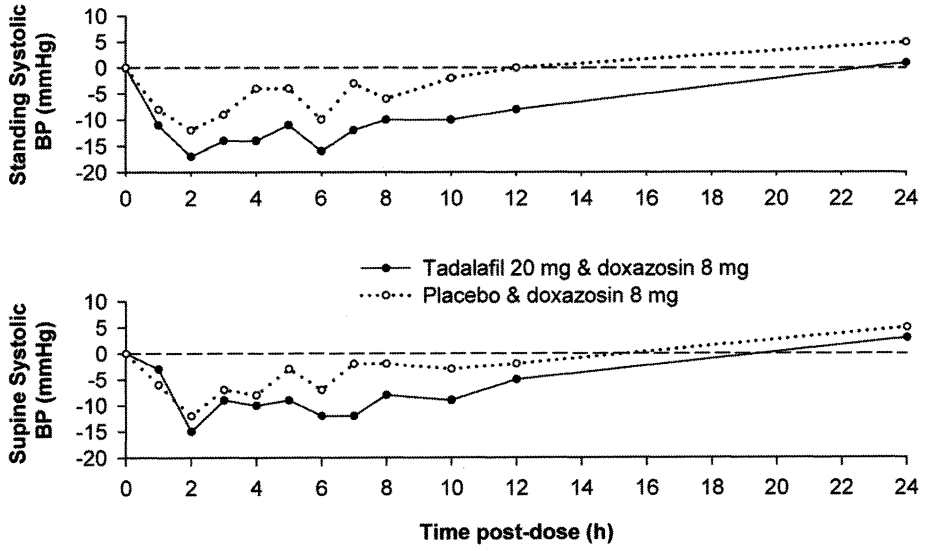


Figure 2: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mm Hg or a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. There were nine and three outliers following administration of tadalafil 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mm Hg, while five and one subject were outliers due to standing systolic BP <85 mm Hg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.

In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover.

In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, tadalafil or placebo were administered at either 8 a.m. or 8 p.m.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in Table 6 and Figure 3.

Table 6: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg at 8 a.m.	Tadalafil 20 mg at 8 p.m.
Ambulatory Blood-Pressure Monitoring (ABPM)	7	8

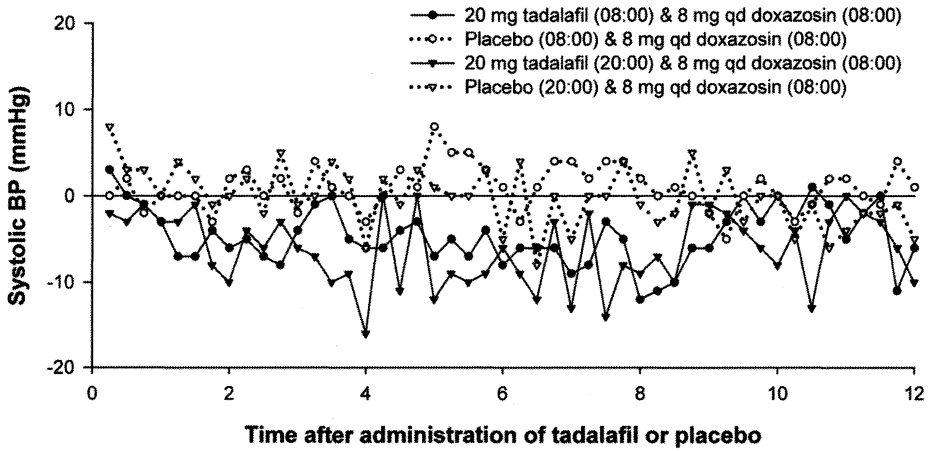


Figure 3: Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure

Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mm Hg were recorded or one or more decreases in systolic blood pressure of >30 mm Hg from a time-matched baseline occurred during the analysis interval.

Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mm Hg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mm Hg following tadalafil and placebo, respectively.

During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mm Hg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mm Hg, following tadalafil and placebo, respectively.

Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.

Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.

In the third doxazosin study, healthy subjects (N=45 treated; 37 completed) received 28 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. After 7 days, doxazosin was initiated at 1 mg and titrated up to 4 mg daily over the last 21 days of each period (7 days on 1 mg; 7 days of 2 mg; 7 days of 4 mg doxazosin). The results are shown in Table 7.

Table 7: Doxazosin Study 3: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		Tadalafil 5 mg
Day 1 of 4 mg Doxazosin	Supine	2.4 (-0.4, 5.2)
	Standing	-0.5 (-4.0, 3.1)
Day 7 of 4 mg Doxazosin	Supine	2.8 (-0.1, 5.7)
	Standing	1.1 (-2.9, 5.0)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours post dose on the first day of each doxazosin dose, (1 mg, 2 mg, 4 mg), as well as on the seventh day of 4 mg doxazosin administration.

Following the first dose of doxazosin 1 mg, there were no outliers on tadalafil 5 mg and one outlier on placebo due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were 2 outliers on tadalafil 5 mg and none on placebo following the first dose of doxazosin 2 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg.

There were no outliers on tadalafil 5 mg and two on placebo following the first dose of doxazosin 4 mg due to a decrease from baseline in standing systolic BP of >30 mm Hg. There was one outlier on tadalafil 5 mg and three on placebo following the first dose of doxazosin 4 mg due to standing systolic BP <85 mm Hg. Following the seventh day of doxazosin 4 mg, there were no outliers on tadalafil 5 mg, one subject on placebo had a decrease >30 mm Hg in standing systolic blood pressure, and one subject on placebo had standing systolic blood pressure <85 mm Hg. All adverse events potentially related to blood pressure effects were rated as mild or moderate. There were two episodes of syncope in this study, one subject following a dose of tadalafil 5 mg alone, and another subject following coadministration of tadalafil 5 mg and doxazosin 4 mg.

Tamsulosin — In the first tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3 period, crossover design to healthy subjects taking 0.4 mg once per day tamsulosin, a selective alpha[1A]-adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing.

Table 8: Tamsulosin (0.4 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 10 mg	Tadalafil 20 mg
Supine	3.2 (-2.3, 8.6)	3.2 (-2.3, 8.7)
Standing	1.7 (-4.7, 8.1)	2.3 (-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.

In the second tamsulosin study, healthy subjects (N=39 treated; and 35 completed) received 14 days of once per day dosing of tadalafil 5 mg or placebo in a two-period crossover design. Daily dosing of tamsulosin 0.4 mg was added for the last seven days of each period.

Table 9: Tamsulosin Study 2: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure		Tadalafil 5 mg
Day 1 of 0.4 mg Tamsulosin	Supine	-0.1 (-2.2, 1.9)
	Standing	0.9 (-1.4, 3.2)
Day 7 of 0.4 mg Tamsulosin	Supine	1.2 (-1.2, 3.6)
	Standing	1.2 (-1.0, 3.5)

Blood pressure was measured manually pre-dose at two time points (-30 and -15 minutes) and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post dose on the first, sixth and seventh days of tamsulosin administration. There were no outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points). One subject on placebo plus tamsulosin (Day 7) and one subject on tadalafil plus tamsulosin (Day 6) had standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood pressure were reported. No syncope was reported.

Alfuzosin — A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.

Table 10: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mm Hg)	Tadalafil 20 mg
Supine	2.2 (-0.9,-5.2)
Standing	4.4 (-0.2, 8.9)

Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

Effects on Blood Pressure When Administered with Antihypertensives

Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Angiotensin II receptor blockers (with and without other antihypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Effects on Exercise Stress Testing

The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the

post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

Effects on Vision

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupilometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics

Three studies were conducted in men to assess the potential effect on sperm characteristics of tadalafil 10 mg (one 6 month study) and 20 mg (one 6 month and one 9 month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

Effects on Cardiac Electrophysiology

The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) -controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QT_c (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QT_c (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

12.3 Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose. Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg and single and once daily multiple doses of 5 mg, from a separate study, (*see* Figure 4) to healthy male subjects are depicted in Figure 4.

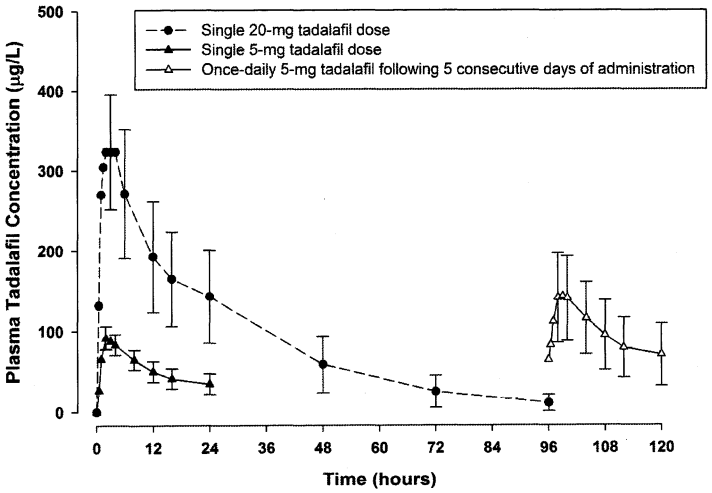


Figure 4: Plasma tadalafil concentrations (mean ± SD) following a single 20-mg tadalafil dose and single and once daily multiple doses of 5 mg

Absorption — After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism — Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Excretion — The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Geriatric — Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered *[see Use in Specific Populations (8.5)]*.

Pediatric — Tadalafil has not been evaluated in individuals less than 18 years old *[see Use in Specific Populations (8.4)]*.

Patients with Diabetes Mellitus — In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Patients with BPH — In patients with BPH following single and multiple-doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and C_{max}) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg.

Mutagenesis — Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

Impairment of Fertility — There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 20 mg.

There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

13.2 Animal Toxicology and/or Pharmacology

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1- and 6-month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood-cell findings were reversible within 2 weeks after stopping treatment.

14 CLINICAL STUDIES

14.1 CIALIS for Use as Needed for ED

The efficacy and safety of tadalafil in the treatment of erectile dysfunction has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. CIALIS, when taken as needed up to once per day, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 7 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12-weeks duration. Two of these studies were conducted in the United States and 5 were conducted in centers outside the US. Additional efficacy and safety studies were performed in ED patients with diabetes mellitus and in patients who developed ED status post bilateral nerve-sparing radical prostatectomy.

In these 7 trials, CIALIS was taken as needed, at doses ranging from 2.5 to 20 mg, up to once per day. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted.

Several assessment tools were used to evaluate the effect of CIALIS on erectile function. The 3 primary outcome measures were the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at the end of a treatment-free baseline period and subsequently at follow-up visits after randomization. The IIEF EF domain has a 30-point total score, where higher scores reflect better erectile function. SEP is a diary in which patients recorded each sexual attempt made throughout the study. SEP Question 2 asks, "Were you able to insert your penis into the partner's vagina?" SEP Question 3 asks, "Did your erection last long enough for you to have successful intercourse?" The overall percentage of successful attempts to insert the penis into the vagina (SEP2) and to maintain the erection for successful intercourse (SEP3) is derived for each patient.

Results in ED Population in US Trials — The 2 primary US efficacy and safety trials included a total of 402 men with erectile dysfunction, with a mean age of 59 years (range 27 to 87 years). The population was 78% White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>90%) patients reported ED of at least 1-year duration. Study A was conducted primarily in academic centers. Study B was conducted primarily in community-based urology practices. In each of these 2 trials, CIALIS 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Table 11). The treatment effect of CIALIS did not diminish over time.

Table 11: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary US Trials

	Study A			Study B		
	Placebo	CIALIS 20 mg		Placebo	CIALIS 20 mg	
	(N=49)	(N=146)	p-value	(N=48)	(N=159)	p-value
EF Domain Score						
Endpoint	13.5	19.5		13.6	22.5	
Change from baseline	-0.2	6.9	<.001	0.3	9.3	<.001
Insertion of Penis (SEP2)						
Endpoint	39%	62%		43%	77%	
Change from baseline	2%	26%	<.001	2%	32%	<.001
Maintenance of Erection (SEP3)						
Endpoint	25%	50%		23%	64%	
Change from baseline	5%	34%	<.001	4%	44%	<.001

Results in General ED Population in Trials Outside the US — The 5 primary efficacy and safety studies conducted in the general ED population outside the US included 1112 patients, with a mean age of 59 years (range 21 to 82 years). The population was 76% White, 1% Black, 3% Hispanic, and 20% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (90%) patients reported ED of at least 1-year duration. In these 5 trials, CIALIS 5, 10, and 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Tables 12, 13 and 14). The treatment effect of CIALIS did not diminish over time.

Table 12: Mean Endpoint and Change from Baseline for the EF Domain of the IIEF in the General ED Population in Five Primary Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				

Endpoint [Change from baseline]	15.0 [0.7]	17.9 [4.0]	20.0 [5.6]	
		p=.006	*p<.001*	
Study D				
Endpoint [Change from baseline]	14.4 [1.1]	17.5 [5.1]	20.6 [6.0]	
		p=.002	*p<.001*	
Study E				
Endpoint [Change from baseline]	18.1 [2.6]		22.6 [8.1]	25.0 [8.0]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	12.7 [-1.6]			22.8 [6.8]
				p<.001
Study G				
Endpoint [Change from baseline]	14.5 [-0.9]		21.2 [6.6]	23.3 [8.0]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 13: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2 ("Were you able to insert your penis into the partner's vagina?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	49% [6%]	57% [15%]	73% [29%]	
		p=.063	*p<.001*	
Study D				
Endpoint [Change from baseline]	46% [2%]	56% [18%]	68% [15%]	
		p=.008	*p<.001*	
Study E				
Endpoint [Change from baseline]	55% [10%]		77% [35%]	85% [35%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	42% [-8%]			81% [27%]
				p<.001
Study G				
Endpoint [Change from baseline]	45% [-6%]		73% [21%]	76% [21%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

Table 14: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 3 ("Did your erection last long enough for you to have successful intercourse?") in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	26% [4%]	38% [19%]	58% [32%]	
		p=.040	*p<.001*	
Study D				
Endpoint [Change from baseline]	28% [4%]	42% [24%]	51% [26%]	
		p<.001	*p<.001*	
Study E				
Endpoint [Change from baseline]	43% [15%]		70% [48%]	78% [50%]
			p<.001	*p<.001*
Study F[a]				
Endpoint [Change from baseline]	27% [1%]			74% [40%]
				p<.001
Study G				
Endpoint [Change from baseline]	32% [5%]		57% [33%]	62% [29%]
			p<.001	*p<.001*

[a] Treatment duration in Study F was 6 months

In addition, there were improvements in EF domain scores, success rates based upon SEP Questions 2 and 3, and patient-reported improvement in erections across patients with ED of all degrees of disease severity while taking CIALIS, compared to patients on placebo.

Therefore, in all 7 primary efficacy and safety studies, CIALIS showed statistically significant improvement in patients' ability to achieve an erection sufficient for vaginal penetration and to maintain the erection long enough for successful intercourse, as measured by the IIEF questionnaire and by SEP diaries.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in all 7 primary efficacy studies in the general ED population (N=235) and in one study that specifically assessed CIALIS in ED patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 15).

Table 15: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in ED Patients with Diabetes

	Placebo	CIALIS 10 mg	CIALIS 20 mg	
	(N=71)	(N=73)	(N=72)	p-value
EF Domain Score				
Endpoint [Change from baseline]	12.2 [0.1]	19.3 [6.4]	18.7 [7.3]	<.001
Insertion of Penis (SEP2)				
Endpoint [Change from baseline]	30% [-4%]	57% [22%]	54% [23%]	<.001
Maintenance of Erection (SEP3)				
Endpoint [Change from baseline]	20% [2%]	48% [28%]	42% [29%]	<.001

Efficacy Results in ED Patients following Radical Prostatectomy — CIALIS was shown to be effective in treating patients who developed ED following bilateral nerve-sparing radical prostatectomy. In 1 randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial in this population (N=303), CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 16).

Table 16: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in Patients who Developed ED Following Bilateral Nerve-Sparing Radical Prostatectomy

	Placebo	CIALIS 20 mg	
	(N=102)	(N=201)	p-value
EF Domain Score			
Endpoint [Change from baseline]	13.3 [1.1]	17.7 [5.3]	<.001
Insertion of Penis (SEP2)			
Endpoint [Change from baseline]	32% [2%]	54% [22%]	<.001
Maintenance of Erection (SEP3)			
Endpoint [Change from baseline]	19% [4%]	41% [23%]	<.001

Results in Studies to Determine the Optimal Use of CIALIS — Several studies were conducted with the objective of determining the optimal use of CIALIS in the treatment of ED. In one of these studies, the percentage of patients reporting successful erections within 30 minutes of dosing was determined. In this randomized, placebo-controlled, double-blinded trial, 223 patients were randomized to placebo, CIALIS 10, or 20 mg. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least 1 erection in 4 attempts that led to successful intercourse. At or prior to 30 minutes, 35% (26/74), 38% (28/74), and 52% (39/75) of patients in the placebo, 10-, and 20-mg groups, respectively, reported successful erections as defined above.

Two studies were conducted to assess the efficacy of CIALIS at a given timepoint after dosing, specifically at 24 hours and at 36 hours after dosing.

In the first of these studies, 348 patients with ED were randomized to placebo or CIALIS 20 mg. Patients were encouraged to make 4 total attempts at intercourse; 2 attempts were to occur at 24 hours after dosing and 2 completely separate attempts were to occur at 36 hours after dosing. The results demonstrated a difference between the placebo group and the CIALIS group at each of the pre-specified timepoints. At the 24-hour timepoint, (more specifically, 22 to

26 hours), 53/144 (37%) patients reported at least 1 successful intercourse in the placebo group versus 84/138 (61%) in the CIALIS 20-mg group. At the 36-hour timepoint (more specifically, 33 to 39 hours), 49/133 (37%) of patients reported at least 1 successful intercourse in the placebo group versus 88/137 (64%) in the CIALIS 20-mg group.

In the second of these studies, a total of 483 patients were evenly randomized to 1 of 6 groups: 3 different dosing groups (placebo, CIALIS 10, or 20 mg) that were instructed to attempt intercourse at 2 different times (24 and 36 hours post-dosing). Patients were encouraged to make 4 separate attempts at their assigned dose and assigned timepoint. In this study, the results demonstrated a statistically significant difference between the placebo group and the CIALIS groups at each of the pre-specified timepoints. At the 24-hour timepoint, the mean, per patient percentage of attempts resulting in successful intercourse were 42, 56, and 67% for the placebo, CIALIS 10-, and 20-mg groups, respectively. At the 36-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 33, 56, and 62% for placebo, CIALIS 10-, and 20-mg groups, respectively.

14.2 CIALIS for Once Daily Use for ED

The efficacy and safety of CIALIS for once daily use in the treatment of erectile dysfunction has been evaluated in 2 clinical trials of 12-weeks duration and 1 clinical trial of 24-weeks duration, involving a total of 853 patients. CIALIS, when taken once daily, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

CIALIS was studied in the general ED population in 2 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12- and 24-weeks duration, respectively. One of these studies was conducted in the United States and one was conducted in centers outside the US. An additional efficacy and safety study was performed in ED patients with diabetes mellitus. CIALIS was taken once daily at doses ranging from 2.5 to 10 mg. Food and alcohol intake were not restricted. Timing of sexual activity was not restricted relative to when patients took Cialis.

Results in General ED Population — The primary US efficacy and safety trial included a total of 287 patients, with a mean age of 59 years (range 25 to 82 years). The population was 86% White, 6% Black, 6% Hispanic, and 2% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>96%) patients reported ED of at least 1-year duration.

The primary efficacy and safety study conducted outside the US included 268 patients, with a mean age of 56 years (range 21 to 78 years). The population was 86% White, 3% Black, 0.4% Hispanic, and 10% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Ninety-three percent of patients reported ED of at least 1-year duration.

In each of these trials, conducted without regard to the timing of dose and sexual intercourse, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 17). When taken as directed, CIALIS was effective at improving erectile function.

In the 6 month double-blind study, the treatment effect of CIALIS did not diminish over time.

Table 17: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two CIALIS for Once Daily Use Studies

	Study H[a]				Study I[b]		
	Placebo	CIALIS 2.5 mg	CIALIS 5 mg		Placebo	CIALIS 5 mg	
	(N=94)	(N=96)	(N=97)	p-value	(N=54)	(N=109)	p-value
EF Domain Score							
Endpoint	14.6	19.1	20.8		15.0	22.8	
Change from baseline	1.2	6.1[c]	7.0[c]	<.001	0.9	9.7[c]	<.001
Insertion of Penis (SEP2)							
Endpoint	51%	65%	71%		52%	79%	
Change from baseline	5%	24%[c]	26%[c]	<.001	11%	37%[c]	<.001
Maintenance of Erection (SEP3)							
Endpoint	31%	50%	57%		37%	67%	
Change from baseline	10%	31%[c]	35%[c]	<.001	13%	46%[c]	<.001

[a] Twenty-four-week study conducted in the US.

[b] Twelve-week study conducted outside the US.

[c] Statistically significantly different from placebo.

Efficacy Results in ED Patients with Diabetes Mellitus — CIALIS for once daily use was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in both studies in the general ED

population (N=79). A third randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design trial included only ED patients with type 1 or type 2 diabetes (N=298). In this third trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (*see* Table 18).

Table 18: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a CIALIS for Once Daily Use Study in ED Patients with Diabetes

	Placebo (N=100)	CIALIS 2.5 mg (N=100)	CIALIS 5 mg (N=98)	p-value
EF Domain Score				
Endpoint	14.7	18.3	17.2	
Change from baseline	1.3	4.8[a]	4.5[a]	<.001
Insertion of Penis (SEP2)				
Endpoint	43%	62%	61%	
Change from baseline	5%	21%[a]	29%[a]	<.001
Maintenance of Erection (SEP3)				
Endpoint	28%	46%	41%	
Change from baseline	8%	26%[a]	25%[a]	<.001

[a] Statistically significantly different from placebo.

14.3 CIALIS 5 mg for Once Daily Use for Benign Prostatic Hyperplasia (BPH)

The efficacy and safety of CIALIS for once daily use for the treatment of the signs and symptoms of BPH was evaluated in 3 randomized, multinational, double-blinded, placebo-controlled, parallel-design, efficacy and safety studies of 12 weeks duration. Two of these studies were in men with BPH and one study was specific to men with both ED and BPH *[see Clinical Studies (14.4)]*. The first study (Study J) randomized 1058 patients to receive either CIALIS 2.5 mg, 5 mg, 10 mg or 20 mg for once daily use or placebo. The second study (Study K) randomized 325 patients to receive either CIALIS 5 mg for once daily use or placebo. The full study population was 87% White, 2% Black, 11% other races; 15% was of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

The primary efficacy endpoint in the two studies that evaluated the effect of CIALIS for the signs and symptoms of BPH was the International Prostate Symptom Score (IPSS), a four week recall questionnaire that was administered at the beginning and end of a placebo run-in period and subsequently at follow-up visits after randomization. The IPSS assesses the severity of irritative (frequency, urgency, nocturia) and obstructive symptoms (incomplete emptying, stopping and starting, weak stream, and pushing or straining), with scores ranging from 0 to 35; higher numeric scores representing greater severity. Maximum urinary flow rate (Q_{max}), an objective measure of urine flow, was assessed as a secondary efficacy endpoint in Study J and as a safety endpoint in Study K.

The results for BPH patients with moderate to severe symptoms and a mean age of 63.2 years (range 44 to 87) who received either CIALIS 5 mg for once daily use or placebo (N=748) in Studies J and K are shown in Table 19 and Figures 5 and 6, respectively.

In each of these 2 trials, CIALIS 5 mg for once daily use resulted in statistically significant improvement in the total IPSS compared to placebo. Mean total IPSS showed a decrease starting at the first scheduled observation (4 weeks) in Study K and remained decreased through 12 weeks.

Table 19: Mean IPSS Changes in BPH Patients in Two CIALIS for Once Daily Use Studies

	Study J			Study K		
	Placebo (N=205)	CIALIS 5 mg (N=205)	p-value	Placebo (N=164)	CIALIS 5 mg (N=160)	p-value
Total Symptom Score (IPSS)						
Baseline	17.1	17.3		16.6	17.1	
Change from Baseline to Week 12	-2.2	-4.8	<.001	-3.6	-5.6	.004

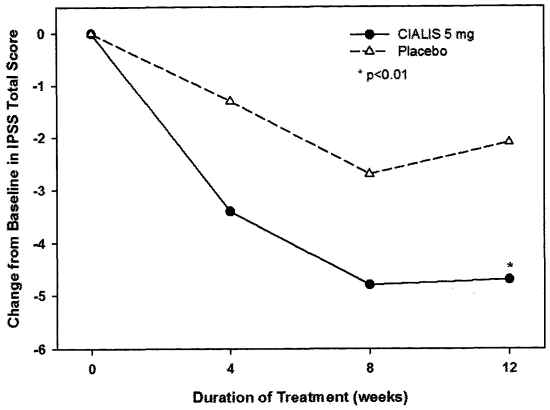


Figure 5: Mean IPSS Changes in BPH Patients by Visit in Study J

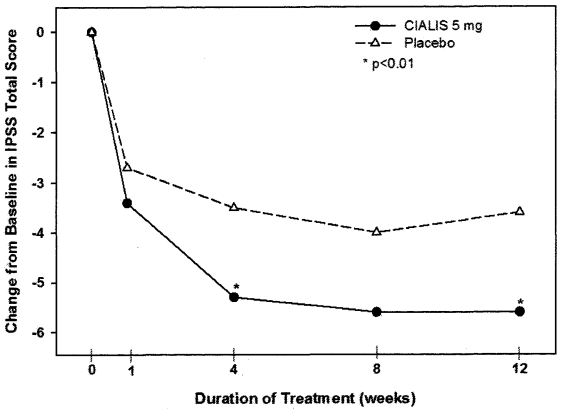


Figure 6: Mean IPSS Changes in BPH Patients by Visit in Study K

In Study J, the effect of CIALIS 5 mg once daily on maximum urinary flow rate (Q_{max}) was evaluated as a secondary efficacy endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

In Study K, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.

Efficacy Results in Patients with BPH initiating CIALIS and Finasteride – CIALIS for once daily use initiated together with finasteride was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate (>30 cc) for up to 26 weeks. This additional double-blinded, parallel-design study of 26 weeks duration randomized 696 men to initiate either CIALIS 5 mg with finasteride 5 mg or placebo with finasteride 5 mg. The study population had a mean age of 64 years (range 46-86). Patients with multiple co-morbid conditions such as erectile dysfunction, diabetes mellitus, hypertension, and other cardiovascular disease were included.

CIALIS with finasteride demonstrated statistically significant improvement in the signs and symptoms of BPH compared to placebo with finasteride, as measured by the total IPSS at 12 weeks, the primary study endpoint (*see* Table 20). Key secondary endpoints demonstrated improvement in total IPSS starting at the first scheduled observation at week 4 (CIALIS -4.0, placebo -2.3: p<.001) and the score remained decreased through 26 weeks (CIALIS -5.5, placebo -4.5; p=.022). However, the magnitude of the treatment difference between placebo/finasteride and CIALIS/finasteride decreased from 1.7 points at Week 4 to 1.0 point at Week 26, as shown in Table 20 and in Figure 7. The incremental benefit of CIALIS beyond 26 weeks is unknown.

Table 20: Mean Total IPSS Changes in BPH Patients in a CIALIS for Once Daily Use Study Together with Finasteride

		Placebo and finasteride 5 mg		CIALIS 5mg and finasteride 5 mg	Treatment difference	

	n	(N=350)[a]	n	(N=345)[a]		p-value[b]
Total Symptom Score (IPSS)						
Baseline[c]	349	17.4	344	17.1		
Change from Baseline to Week 4[b]	340	-2.3	330	-4.0	-1.7	<.001
Change from Baseline to Week 12[b]	318	-3.8	317	-5.2	-1.4	.001
Change from Baseline to Week 26[b]	295	-4.5	308	-5.5	-1.0	.022

[a] Overall ITT population.
[b] Mixed model for repeated measurements.
[c] Unadjusted mean.

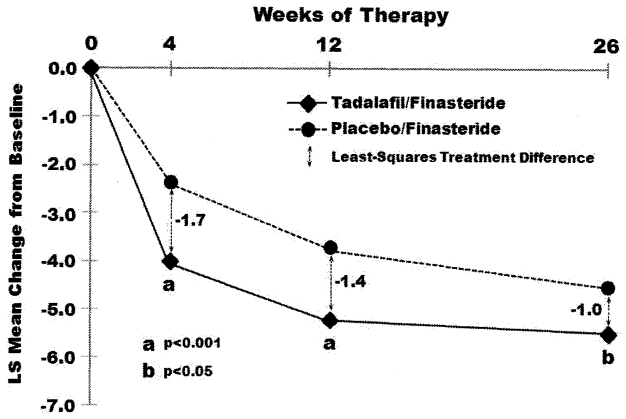


Figure 7: Mean Total IPSS Changes By Visit in BPH Patients Taking CIALIS for Once Daily Use Together With Finasteride

In the 404 patients who had both ED and BPH at baseline, changes in erectile function were assessed as key secondary endpoints using the EF domain of the IIEF questionnaire. CIALIS with finasteride (N=203) was compared to placebo with finasteride (N=201). A statistically significant improvement from baseline (CIALIS/finasteride 13.7, placebo/finasteride 15.1) was observed at week 4 (CIALIS/finasteride 3.7, placebo/finasteride -1.1; p<.001), week 12 (CIALIS/finasteride 4.7, placebo/finasteride 0.6; p<.001), and week 26 (CIALIS/finasteride 4.7, placebo/finasteride 0.0; p<.001).

14.4 CIALIS 5 mg for Once Daily Use for ED and BPH

The efficacy and safety of CIALIS for once daily use for the treatment of ED, and the signs and symptoms of BPH, in patients with both conditions was evaluated in one placebo-controlled, multinational, double-blind, parallel-arm study which randomized 606 patients to receive either CIALIS 2.5 mg, 5 mg, for once daily use or placebo. ED severity ranged from mild to severe and BPH severity ranged from moderate to severe. The full study population had a mean age of 63 years (range 45 to 83) and was 93% White, 4% Black, 3% other races; 16% were of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

In this study, the co-primary endpoints were total IPSS and the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF). One of the key secondary endpoints in this study was Question 3 of the Sexual Encounter Profile diary (SEP3). Timing of sexual activity was not restricted relative to when patients took CIALIS.

The efficacy results for patients with both ED and BPH, who received either CIALIS 5 mg for once daily use or placebo (N=408) are shown in Tables 21 and 22 and Figure 8.

CIALIS 5 mg for once daily use resulted in statistically significant improvements in the total IPSS and in the EF domain of the IIEF questionnaire. CIALIS 5 mg for once daily use also resulted in statistically significant improvement in SEP3. CIALIS 2.5 mg did not result in statistically significant improvement in the total IPSS.

Table 21: Mean IPSS and IIEF EF Domain Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	p-value
Total Symptom Score (IPSS)			
	(N=193)	**(N=206)**	
Baseline	18.2	18.5	
Change from Baseline to Week 12	-3.8	-6.1	<.001
EF Domain Score (IIEF EF)			
	(N=188)	**(N=202)**	
Baseline	15.6	16.5	
Endpoint	17.6	22.9	
Change from Baseline to Week 12	1.9	6.5	<.001

Table 22: Mean SEP Question 3 Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	
	(N=187)	**(N=199)**	**p-value**
Maintenance of Erection (SEP3)			
Baseline	36%	43%	
Endpoint	48%	72%	
Change from Baseline to Week 12	12%	32%	<.001

CIALIS for once daily use resulted in improvement in the IPSS total score at the first scheduled observation (week 2) and throughout the 12 weeks of treatment (*see* Figure 8).

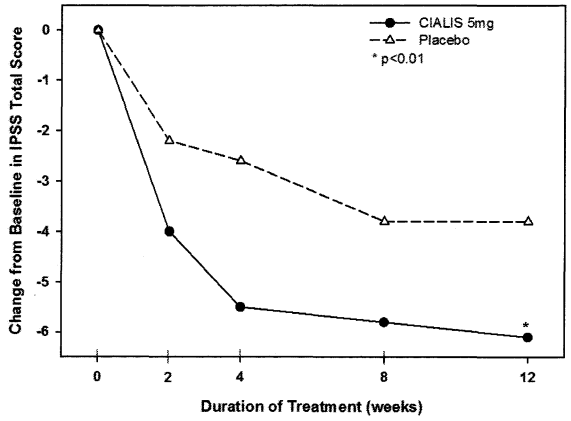


Figure 8: Mean IPSS Changes in ED/BPH Patients by Visit in Study L

In this study, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CIALIS (tadalafil) is supplied as follows:

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow, and supplied in the following package sizes:

2.5 mg tablets debossed with "C 2 1/2"
Blisters of 2 x 15 NDC 0002-4465-34
5 mg tablets debossed with "C 5"
Bottles of 30 NDC 0002-4462-30

Blisters of 2 x 15 NDC 0002-4462-34
10 mg tablets debossed with "C 10"
Bottles of 30 NDC 0002-4463-30
20 mg tablets debossed with "C 20"
Bottles of 30 NDC 0002-4464-30

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)"

17.1 Nitrates

Physicians should discuss with patients the contraindication of CIALIS with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of CIALIS with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

17.2 Cardiovascular Considerations

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Physicians should advise patients who experience symptoms upon initiation of sexual activity to refrain from further sexual activity and seek immediate medical attention *[see Warnings and Precautions (5.1)]*.

17.3 Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.4 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing CIALIS for once daily use, especially the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and potent inhibitors of cytochrome P450 3A4) and with substantial consumption of alcohol. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), Drug Interactions (7.1, 7.2), Clinical Pharmacology (12.2), and Clinical Studies (14.2)]*.

17.5 Priapism

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.

17.6 Vision

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors *[see Warnings and Precautions (5.4) and Adverse Reactions (6.2)]*.

17.7 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6.1, 6.2)]*.

17.8 Alcohol

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Warnings and Precautions (5.9), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.9 Sexually Transmitted Disease

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

17.10 Recommended Administration

Physicians should instruct patients on the appropriate administration of CIALIS to allow optimal use.

For CIALIS for use as needed in men with ED, patients should be instructed to take one tablet at least 30 minutes before anticipated sexual activity. In most patients, the ability to have sexual intercourse is improved for up to 36 hours.

For CIALIS for once daily use in men with ED or ED/BPH, patients should be instructed to take one tablet at approximately the same time every day without regard for the timing of sexual activity. Cialis is effective at improving erectile function over the course of therapy.

For CIALIS for once daily use in men with BPH, patients should be instructed to take one tablet at approximately the same time every day.

Revision Date 10/2013

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

www.cialis.com

PV 6605 AMP

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg tadalafil.

Excipient(s) with known effect:
Each coated tablet contains 87 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light orange-yellow and almond shaped tablets, marked "C 2 ½" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

Posology
Adult men
In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.
In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Special populations

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (see sections 4.4 and 5.2).

Men with hepatic impairment
The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (see sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
There is no relevant use of CIALIS in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration
CIALIS is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated. (see section 4.5).

CIALIS, must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:
- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

CIALIS is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Before treatment with CIALIS

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CIALIS, to sexual activity, or to a combination of these or other factors.

In patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In patients who are taking alpha$_1$ blockers, concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision
Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Renal and hepatic impairment
Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of CIALIS is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

CIALIS, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing CIALIS to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

CIALIS and other treatments for erectile dysfunction
The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take CIALIS in such combinations.

Lactose
CIALIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4).
Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88 %, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of CIALIS (2.5 mg-20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol).

Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

CIALIS is not indicated for use by women.

Pregnancy
There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of CIALIS during pregnancy.

Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. CIALIS should not be used during breast feeding.

Fertility
Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

CIALIS has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to CIALIS, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in

which the incidences increase with increasing dose of CIALIS. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7116 patients on CIALIS and 3718 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			

	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia, Gastro-oesophageal reflux	Abdominal pain	
Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2],
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Penile haemorrhage, Haematospermia	Prolonged erections, Priapism[2]
General disorders and administration site conditions			
		Chest pain[1]	Facial oedema[2], Sudden cardiac death[1, 2]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects
Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4 enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety
Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to CIALIS on demand. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Tadalafil at doses of 2.5, 5, and 10 mg taken once a day was initially evaluated in 3 clinical studies involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67 % on CIALIS 5 mg, 50 % on CIALIS 2.5 mg as compared to 31 and 37 % with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of

successful attempts were 41 and 46 % on CIALIS 5 mg and 2.5 mg, respectively, as compared to 28 % with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naïve to PDE5 inhibitors were randomized to CIALIS 5 mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68 % for CIALIS patients compared to 52 % for patients on placebo.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48 % as compared to 17 % with placebo.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus CIALIS may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special populations

Elderly

Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If CIALIS is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.
There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
croscarmellose sodium,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:
lactose monohydrate,
hypromellose,
triacetin,
titanium dioxide (E171),
iron oxide yellow (E172),

iron oxide red (E172),
talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 28 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002
Date of last renewal: 12 November 2012

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. NAME OF THE MEDICINAL PRODUCT

CIALIS 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg tadalafil.

Excipient(s) with known effect:
Each coated tablet contains 121 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow and almond shaped tablets, marked "C 5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

Posology
Erectile dysfunction in adult men
In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.
In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Benign prostatic hyperplasia in adult men
The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

Special populations
Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose for on-demand treatment.

Once-a-day dosing of 2.5 or 5 mg tadalafil both for the treatment of erectile dysfunction or benign prostatic hyperplasia is not recommended in patients with severe renal impairment. (see sections 4. 4 and 5.2).

Men with hepatic impairment
For the treatment of erectile dysfunction using on-demand CIALIS the recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Once-a-day dosing of CIALIS both for the treatment of erectile dysfunction and benign prostatic hyperplasia has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (see sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
There is no relevant use of CIALIS in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration
CIALIS is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated. (see section 4.5).

CIALIS, must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:
- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

CIALIS is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Before treatment with CIALIS
A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3).

Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CIALIS, to sexual activity, or to a combination of these or other factors.

In patients receiving concomitant antihypertensive medicinal products, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

In patients who are taking alpha$_1$ blockers, concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Renal and hepatic impairment
Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of CIALIS is not recommended in patients with severe renal impairment.

There are limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration either for the treatment of erectile dysfunction or benign prostatic hyperplasia has not been evaluated in patients with hepatic insufficiency. If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

CIALIS, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing CIALIS to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

CIALIS and other treatments for erectile dysfunction
The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take CIALIS in such combinations.

Lactose
CIALIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4).

Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88 %, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of CIALIS (2.5 mg-20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

CIALIS is not indicated for use by women.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of CIALIS during pregnancy.

Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. CIALIS should not be used during breast feeding.

Fertility
Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

CIALIS has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to CIALIS, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of CIALIS. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7116 patients on CIALIS and 3718 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2],

			Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia, Gastro-oesophageal reflux	Abdominal pain	
Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2]
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Penile haemorrhage, Haematospermia	Prolonged erections, Priapism[2]
General disorders and administration site conditions			
		Chest pain[1]	Facial oedema[2], Sudden cardiac

			death[1,2]

(1)Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action
Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

Pharmacodynamic effects
Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac

contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Erectile dysfunction

For CIALIS on demand, three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48% as compared to 17% with placebo.

For once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67 % on CIALIS 5 mg, 50 % on CIALIS 2.5 mg as compared to 31 and 37 % with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46 % on CIALIS 5 mg and 2.5 mg, respectively, as compared to 28 % with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naïve to PDE5 inhibitors were randomized to CIALIS 5 mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68 % for CIALIS patients compared to 52 % for patients on placebo.

Benign prostatic hyperplasia

CIALIS was studied in 4 clinical studies of 12 weeks duration enrolling over 1500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with CIALIS 5mg in the four studies were -4.8, -5.6, -6.1 and -6.3 compared to -2.2, -3.6, -3.8 and -4.2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0.4 mg as an active comparator, the improvement in total international prostate symptom score with CIALIS 5mg, tamsulosin and placebo were -6.3, -5.7 and -4.2 respectively.

One of these studies assessed improvements in erectile dysfunction and signs and symptoms of benign prostatic hyperplasia in patients with both conditions. The improvements in the erectile function domain of the international index of erectile function and the total international prostate symptom score in this study were 6.5 and -6.1 with CIALIS 5 mg compared to 1.8 and -3.8 with placebo, respectively. The mean per-subject proportion of successful sexual intercourse attempts was 71.9% with CIALIS 5 mg compared to 48.3% with placebo.

The maintenance of the effect was evaluated in an open-label extension to one of the studies, which showed that the improvement in total international prostate symptom score seen at 12 weeks was maintained for up to 1 additional year of treatment with CIALIS 5mg.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus CIALIS may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special populations

Elderly

Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If CIALIS is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.
There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
croscarmellose sodium,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:
lactose monohydrate,
hypromellose,
triacetin,
titanium dioxide (E171),
iron oxide yellow (E172),

talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 14, 28 or 84 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/007-008, 010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002
Date of last renewal: 12 November 2012

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. NAME OF THE MEDICINAL PRODUCT

CIALIS 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg tadalafil.

Excipient(s) with known effect:
Each coated tablet contains 170 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow and almond shaped tablets, marked "C 10" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

Posology
Adult men
In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.
In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Special populations

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (see sections 4.4 and 5.2)

Men with hepatic impairment
The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (see sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

Paediatric population
There is no relevant use of CIALIS in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration
CIALIS is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated. (see section 4.5).

CIALIS, must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:
- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

CIALIS is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Before treatment with CIALIS

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CIALIS, to sexual activity, or to a combination of these or other factors.

In patients who are taking alpha$_1$ blockers, concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision
Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Hepatic impairment
There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

CIALIS, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing CIALIS to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

CIALIS and other treatments for erectile dysfunction
The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take CIALIS in such combinations.

Lactose

CIALIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4).
Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88 %, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of CIALIS (2.5 mg – 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not

inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

CIALIS is not indicated for use by women.

Pregnancy
There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of CIALIS during pregnancy.

Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. CIALIS should not be used during breast feeding.

Fertility
Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

CIALIS has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to CIALIS, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of CIALIS. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7116 patients on CIALIS and 3718 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain,	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia, Gastro-oesophageal reflux	Abdominal pain	

Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2]
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Penile haemorrhage, Haematospermia	Prolonged erections, Priapism[2]
General disorders and administration site conditions			
		Chest pain[1]	Facial oedema[2], Sudden cardiac death[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to CIALIS. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81 % of patients reported that CIALIS improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking CIALIS (86 %, 83 %, and 72 % for mild, moderate, and severe, respectively, as compared to 45 %, 42 %, and 19 % with placebo). In the primary efficacy studies, 75 % of intercourse attempts were successful in CIALIS treated patients as compared to 32 % with placebo.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48 % as compared to 17 % with placebo.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus CIALIS may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special populations

Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.
There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
croscarmellose sodium,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:
lactose monohydrate,
hypromellose,
triacetin,
titanium dioxide (E171),
iron oxide yellow (E172),
talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 4 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002
Date of last renewal: 12 November 2012

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. NAME OF THE MEDICINAL PRODUCT

CIALIS 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg tadalafil.

Excipient(s) with known effect:
Each coated tablet contains 233 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow and almond shaped tablets, marked "C 20" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

Posology
Adult men
In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried.

It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Special populations

Elderly men

Dose adjustments are not required in elderly patients.

Men with renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (see sections 4.4 and 5.2)

Men with hepatic impairment

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (see sections 4.4 and 5.2).

Men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of CIALIS in the paediatric population with regard to the treatment of erectile dysfunction.

Method of administration

CIALIS is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated. (see section 4.5).

CIALIS, must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- patients with myocardial infarction within the last 90 days,
- patients with unstable angina or angina occurring during sexual intercourse,
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,
- patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

CIALIS is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Before treatment with CIALIS
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CIALIS, to sexual activity, or to a combination of these or other factors.

In patients who are taking alpha$_1$ blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision
Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Hepatic impairment
There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

CIALIS, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing CIALIS to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

CIALIS and other treatments for erectile dysfunction
The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take CIALIS in such combinations.

Lactose

CIALIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on tadalafil

Cytochrome P450 inhibitors
Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4). Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of drug interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88 %, relative to the AUC values for tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of CIALIS (2.5 mg – 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40 % alcohol [vodka] in an 80-kg male) but in some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products
Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not

inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

CIALIS is not indicated for use by women.

Pregnancy
There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of CIALIS during pregnancy.

Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. CIALIS should not be used during breast feeding.

Fertility
Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

CIALIS has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to CIALIS, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia are headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of CIALIS.. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7116 patients on CIALIS and 3718 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common	Common	Uncommon	Rare
Immune system disorders			
		Hypersensitivity reactions	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia, Gastro-oesophageal reflux	Abdominal pain	

Skin and subcutaneous tissue disorders			
		Rash, Hyperhydrosis (sweating)	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2]
Musculoskeletal, connective tissue and bone disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Penile haemorrhage, Haematospermia	Prolonged erections, Priapism[2]
General disorders and administration site conditions			
		Chest pain[1]	Facial oedema[2], Sudden cardiac death[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.
In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to CIALIS. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81 % of patients reported that CIALIS improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking CIALIS (86 %, 83 %, and 72 % for mild, moderate, and severe, respectively, as compared to 45 %, 42 %, and 19 % with placebo). In the primary efficacy studies, 75 % of intercourse attempts were successful in CIALIS treated patients as compared to 32 % with placebo.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible-dose, on demand) of 48 % as compared to 17 % with placebo.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, thus CIALIS may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Special populations

Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency
In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.
There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.
There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7 – 18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate,
croscarmellose sodium,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:
lactose monohydrate,
hypromellose,
triacetin,
titanium dioxide (E171),
iron oxide yellow (E172),
talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 2, 4, 8, 10 and 12 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/002-005, 009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002
Date of last renewal: 12 November 2012

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.

TADALAFIL: Core Data Sheet

ザルティア錠 5 mg
ザルティア錠 2.5 mg

1.7　同種同効品一覧表

日本イーライリリー株式会社

目次

1.7 同種同効品一覧表

表 1.7-1 同種同効品一覧表

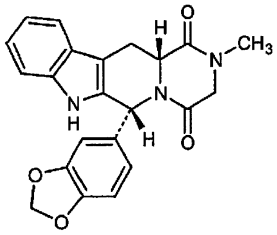
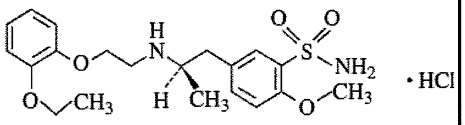
一般的名称	タダラフィル	タムスロシン塩酸塩
販売名	ザルティア錠 2.5 mg ザルティア錠 5 mg	ハルナール D 錠 0.1 mg ハルナール D 錠 0.2 mg
会社名	日本イーライリリー株式会社	アステラス製薬株式会社
承認年月日	－	2004 年 9 月 16 日
再評価 年月日 再審査 年月日	－	再審査：2003 年 11 月 25 日（ハルナール カプセルとして）
規制区分	処方せん医薬品 （注意－医師等の処方せんにより使用すること）	処方せん医薬品 （注意－医師等の処方せんにより使用すること）
化学構造式		
剤型・含量	フィルムコート錠 1 錠中：タダラフィルとして 2.5 mg 1 錠中：タダラフィルとして 5 mg	口腔内崩壊錠 1 錠中：日局タムスロシン塩酸塩 0.1 mg 1 錠中：日局タムスロシン塩酸塩 0.2 mg
効能・効果	前立腺肥大症に伴う排尿障害	前立腺肥大症に伴う排尿障害
効能・効果に関連する使用上の注意	本剤の適用にあたっては、前立腺肥大症の診断・診療に関する国内外のガイドライン等の最新の情報を参考に、適切な検査により診断を確定すること。	－
用法・用量	通常、成人には 1 日 1 回タダラフィルとして 5 mg を経口投与する。	通常、成人にはタムスロシン塩酸塩として 0.2 mg を 1 日 1 回食後に経口投与する。 なお、年齢、症状により適宜増減する。
用法・用量に関連する使用上の注意	1. 中等度の腎障害のある患者では、本剤の血漿中濃度が上昇する可能性があること及び投与経験が限られていることから、患者の状態を観察しながら 1 日 1 回 2.5 mg から投与を開始するなども考慮すること。［「薬物動態」の項参照］ 2. チトクローム P450 3A4（CYP3A4）を強く阻害する薬剤を投与中の患者では、本剤の血漿中濃度が上昇することが認められているので、1 日 1 回 2.5 mg から投与を開始し、患者の状態を観察しながら適宜 5 mg へ増量すること。［「相互作用」の項参照］	－

表 1.7-1 同種同効品一覧表 （続き）

一般的名称	タダラフィル	タムスロシン塩酸塩
使用上の注意	**【警告】** **1. 本剤と硝酸剤又は一酸化窒素（NO）供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）との併用により降圧作用が増強し、過度に血圧を下降させることがあるので、本剤投与の前に、硝酸剤又は一酸化窒素（NO）供与剤が投与されていないことを十分確認し、本剤投与中及び投与後においても硝酸剤又は一酸化窒素（NO）供与剤が投与されないよう十分注意すること。［「禁忌」の項参照］** **2. 死亡例を含む心筋梗塞等の重篤な心血管系等の有害事象が報告されているので、本剤投与の前に、心血管系障害の有無等を十分確認すること。［「禁忌」の項及び「副作用」の項参照］**	－
	【禁忌（次の患者には投与しないこと）】 **1. 本剤の成分に対し過敏症の既往歴のある患者** **2. 硝酸剤又は一酸化窒素（NO）供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）を投与中の患者［「相互作用」の項参照］** **3. 次に掲げる心血管系障害を有する患者［「その他の注意」の項参照。また、これらの患者に対する使用経験がない。］** **(1)不安定狭心症のある患者** **(2)心不全（NYHA 分類 III 度以上）のある患者** **(3)コントロール不良の不整脈、低血圧（血圧＜90/50 mmHg）又はコントロール不良の高血圧（安静時血圧＞170/100 mmHg）のある患者** **(4)心筋梗塞の既往歴が最近 3 ヵ月以内にある患者** **(5)脳梗塞・脳出血の既往歴が最近 6 ヵ月以内にある患者** **4. 重度の腎障害のある患者［重度の腎障害のある患者では本剤の血漿中濃度が上昇すること及び使用経験が限られているため。（「薬物動態」の項参照）］** **5. 重度の肝障害のある患者［重度の肝障害のある患者における使用経験がないため。］**	**【禁忌（次の患者には投与しないこと）】** 本剤の成分に対し過敏症の既往歴のある患者

表 1.7-1 同種同効品一覧表 （続き）

一般的名称	タダラフィル	タムスロシン塩酸塩
使用上の注意	**1. 慎重投与（次の患者には慎重に投与すること）** (1) α 遮断剤を投与中の患者［「相互作用」の項参照］ (2) 軽度・中等度の腎障害のある患者［「薬物動態」の項参照］ (3) 軽度・中等度の肝障害のある患者［投与経験が限られている。］ (4) ホスホジエステラーゼ（PDE）5 阻害剤を投与中の患者［PDE5 阻害剤との併用使用の経験がない。］ (5) 高齢者［「高齢者への投与」の項参照］ (6) 陰茎の構造上欠陥（屈曲、陰茎の線維化、Peyronie 病等）のある患者［本剤の薬理作用により勃起が起こり、その結果陰茎に痛みを引き起こす可能性がある。］ (7) 持続勃起症の素因となり得る疾患（鎌状赤血球性貧血、多発性骨髄腫、白血病等）のある患者 (8) 出血性疾患又は消化性潰瘍のある患者［*in vitro* 試験でニトロプルシドナトリウム（NO 供与剤）の血小板凝集抑制作用を増強することが認められている。出血性疾患又は消化性潰瘍のある患者に対する安全性は確立していない。］ (9) 網膜色素変性症患者［網膜色素変性症の患者には PDE の遺伝的障害を持つ症例が少数認められる。］	**1. 慎重投与（次の患者には慎重に投与すること）** (1) 起立性低血圧のある患者［症状が悪化するおそれがある。］ (2) 重篤な肝機能障害のある患者［血漿中濃度が上昇するおそれがある。］ (3) 重篤な腎機能障害のある患者［血漿中濃度が上昇するおそれがある。（「薬物動態」の項参照）］ (4) 高齢者（「高齢者への投与」の項参照） (5) ホスホジエステラーゼ 5 阻害作用を有する薬剤を服用している患者（「相互作用」の項参照）
	2. 重要な基本的注意 (1) 他の PDE5 阻害剤と同様に、本剤は血管拡張作用を有するため一過性の軽度の血圧低下があらわれる場合がある。本剤投与の前に、心血管系障害の有無等を十分確認すること。 (2) α 遮断剤と併用する場合は、降圧作用を増強するおそれがあるため、患者背景を考慮して治療上の有益性が危険性を上回る場合にのみ慎重に投与すること。［「相互作用」の項参照］ (3) 4 時間以上の勃起の延長又は持続勃起（6 時間以上持続する痛みを伴う勃起）が外国にてごくまれに報告されている。持続勃起に対する処置を速やかに行わないと陰茎組織の損傷又は勃起機能を永続的に損なうことがあるので、勃起が 4 時間以上持続する症状がみられた場合、直ちに医師の診断を受けるよう指導すること。 (4) 本剤投与後に急激な視力低下又は急激な視力喪失があらわれた場合には、速やかに眼科専門医の診察を受けるよう、患者に指導すること。［「その他の注意」の項参照］	**2. 重要な基本的注意** (1) 本剤は口腔内で崩壊するが、口腔の粘膜から吸収されることはないため、唾液又は水で飲み込ませること。 (2) 本剤の過剰投与により**血圧低下**が予想されるので、投与量には注意すること。 (3) **立位血圧が低下**することがあるので、体位変換による血圧変化に注意すること。 (4) 本剤による治療は原因療法ではなく、対症療法であることに留意し、本剤投与により期待する効果が得られない場合は、手術療法等、他の適切な処置を考慮すること。 (5) **めまい等**があらわれることがあるので、高所作業、自動車の運転等**危険を伴う作業に従事する場合には注意させる**こと。 (6) 本剤投与開始時に**降圧剤投与の有無**について問診を行い、降圧剤が投与されている場合には血圧変化に注意し、血圧低下がみられたときには、減量又は中止するなど適切な処置を行うこと。

表 1.7-1 同種同効品一覧表 （続き）

<table>
<tr><th>一般的名称</th><th>タダラフィル</th><th>タムスロシン塩酸塩</th></tr>
<tr><td>使用上の注意</td><td>(5)　臨床試験において、めまいや視覚障害が認められているので、高所作業、自動車の運転等危険を伴う機械を操作する際には注意させること。
(6)　本剤投与後に急激な聴力低下又は突発性難聴（耳鳴り、めまいを伴うことがある）があらわれた場合には、速やかに耳鼻科専門医の診察を受けるよう、患者に指導すること。［「副作用」の項及び「その他の注意」の項参照］
(7)　国内において他の前立腺肥大症治療薬と併用した際の臨床効果は確認されていない。
(8)　本剤による治療は原因療法ではなく、対症療法であることに留意し、本剤投与により期待する効果が得られない場合は、手術療法等、他の適切な処置を考慮すること。</td><td></td></tr>
<tr><td></td><td>3.　相互作用
本剤は主に CYP3A4 により代謝される。
(1) 併用禁忌（併用しないこと）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>硝酸剤及び NO 供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）</td><td>併用により、降圧作用を増強するとの報告がある。</td><td>NO は cGMP の産生を刺激し、一方、本剤は cGMP の分解を抑制することから、両剤の併用により cGMP の増大を介する NO の降圧作用が増強する。</td></tr>
</table>
(2) 併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>CYP3A4 阻害剤（イトラコナゾール、クラリスロマイシン、テラプレビル、グレープフルーツジュース等）</td><td>強い CYP3A4 阻害作用を有するケトコナゾール（経口剤、国内未発売）との併用により、本剤の AUC 及び C_{max} が 312%及び 22%増加するとの報告がある。［「薬物動態」の項参照］</td><td>CYP3A4 阻害によるクリアランスの減少。</td></tr>
<tr><td>HIV プロテアーゼ阻害剤（リトナビル、インジナビル、サキナビル、ダルナビル等）</td><td>リトナビルとの併用により、本剤の AUC が 124%増加するとの報告がある。［「薬物動態」の項参照］</td><td></td></tr>
<tr><td>CYP3A4 誘導剤（リファンピシン、フェニトイン、フェノバルビタール等）</td><td>リファンピシンとの併用により、本剤の AUC 及び C_{max} がそれぞれ 88%及び 46%低下するとの報告がある。</td><td>CYP3A4 誘導によるクリアランスの増加により本剤の血漿中濃度が低下し、本剤の効果が減弱するおそれがある。</td></tr>
</table></td><td>3.　相互作用
併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>降圧剤</td><td>起立性低血圧が起こるおそれがあるので、減量するなど注意すること。</td><td>降圧剤服用中の患者は起立時の血圧調節力が低下している場合がある。</td></tr>
<tr><td>ホスホジエステラーゼ 5 阻害作用を有する薬剤
シルデナフィルクエン酸塩
バルデナフィル塩酸塩水和物
等</td><td>併用により症候性低血圧があらわれるとの報告がある。</td><td>本剤はα遮断作用を有するため、併用によりこれらの血管拡張作用による降圧作用を増強するおそれがある。</td></tr>
</table></td></tr>
</table>

表 1.7-1 同種同効品一覧表 （続き）

<table>
<tr><td>一般的名称</td><td>タダラフィル</td><td>タムスロシン塩酸塩</td></tr>
<tr><td>使用上の注意</td><td>
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>α遮断剤（ドキサゾシン、テラゾシン等）</td><td>ドキサゾシンとの併用により、立位収縮期血圧及び拡張期血圧は最大それぞれ 9.81 mmHg 及び 5.33 mmHg 下降するとの報告がある。［「薬物動態」の項参照］また、α遮断剤との併用で失神等の症状を伴う血圧低下を来したとの報告がある。</td><td rowspan="3">本剤は血管拡張作用による降圧作用を有するため、併用により降圧作用を増強するおそれがある。</td></tr>
<tr><td>降圧剤（アムロジピン、メトプロロール、エナラプリル、カンデサルタン等）</td><td>アンジオテンシンII受容体拮抗剤（単剤又は多剤）との併用により、自由行動下収縮期血圧及び拡張期血圧は最大それぞれ 8 mmHg 及び 4 mmHg 下降するとの報告がある。</td></tr>
<tr><td>カルペリチド</td><td>併用により降圧作用が増強するおそれがある。</td></tr>
</table>
4. 副作用
承認時までに、日本を含むアジアで実施されたプラセボ対照二重盲検並行群間比較試験（3 試験）において、本剤を投与された総症例 894 例（日本人患者 680 例を含む）中 98 例（11.0%）に副作用が認められた。主な副作用は、消化不良 15 例（1.7%）、頭痛 12 例（1.3%）、CK（CPK）上昇 8 例（0.9%）、筋肉痛 8 例（0.9%）、ほてり 8 例（0.9%）等であった。
(1) 重大な副作用
過敏症（発疹、蕁麻疹、顔面浮腫、剥脱性皮膚炎、Stevens-Johnson 症候群）（頻度不明）：本剤の投与により（男性勃起不全治療剤及び肺動脈性肺高血圧症治療剤としての投与を含む）、発疹、蕁麻疹、顔面浮腫、剥脱性皮膚炎、Stevens-Johnson 症候群等の過敏症が、ごくまれに報告されている。このような症状が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。</td><td>4. 副作用
ハルナールカプセル承認時及び市販後の使用成績調査における調査症例 4,724 例中、ハルナールカプセルとの関連が疑われる副作用（臨床検査値異常を含む）は 104 例（2.2%）に発現し、主なものはめまい、胃不快感等であった。
（ハルナールカプセル再審査結果通知：2003 年 11 月）
(1) 重大な副作用
1) 失神・意識喪失（頻度不明）：血圧低下に伴う一過性の意識喪失等があらわれることがあるので、観察を十分に行い、異常が認められた場合には、本剤の投与を中止し適切な処置を行うこと。
2) 肝機能障害、黄疸（いずれも頻度不明）：AST（GOT）上昇、ALT（GPT）上昇、黄疸等があらわれることがあるので、観察を十分に行い、異常が認められた場合には、本剤の投与を中止するなど、適切な処置を行うこと。</td></tr>
</table>

表 1.7-1 同種同効品一覧表 （続き）

<table>
<tr><td>一般的名称</td><td>タダラフィル</td><td>タムスロシン塩酸塩</td></tr>
<tr><td rowspan="3">使用上の注意</td><td>(2) その他の副作用
<table><tr><th>副作用分類</th><th>1%以上</th><th>1%未満</th><th>頻度不明注1)</th></tr><tr><td>循環器</td><td></td><td>動悸、ほてり、潮紅</td><td>心筋梗塞、胸痛、心突然死、失神、低血圧</td></tr><tr><td>感覚器</td><td></td><td></td><td>眼痛、霧視、結膜充血、網膜動脈閉塞、網膜静脈閉塞、眼瞼腫脹、視野欠損、非動脈炎性前部虚血性視神経症、突発性難聴</td></tr><tr><td>消化器</td><td>消化不良</td><td>胃食道逆流性疾患、下痢、胃炎</td><td>腹痛</td></tr><tr><td>腎臓</td><td></td><td>腎クレアチニン・クリアランス減少</td><td></td></tr><tr><td>筋骨格</td><td></td><td>筋肉痛、背部痛</td><td>四肢痛</td></tr><tr><td>精神・神経系</td><td>頭痛</td><td>浮動性めまい</td><td>片頭痛、脳卒中</td></tr><tr><td>泌尿・生殖器</td><td></td><td>勃起増強、自発陰茎勃起</td><td>持続勃起症、勃起の延長</td></tr><tr><td>呼吸器</td><td></td><td></td><td>呼吸困難、鼻出血</td></tr><tr><td>皮膚</td><td></td><td></td><td>多汗症</td></tr><tr><td>その他</td><td></td><td>CK(CPK)上昇</td><td></td></tr></table>注 1）自発報告等を含む情報であるため、頻度不明。</td><td>(2) その他の副作用
<table><tr><th></th><th>0.1～5%未満</th><th>0.1%未満</th><th>頻度不明</th></tr><tr><td>精神神経系</td><td>めまい、ふらふら感</td><td>立ちくらみ、頭痛、眠気</td><td>いらいら感、しびれ感</td></tr><tr><td>循環器</td><td></td><td>血圧低下、起立性低血圧、頻脈、動悸</td><td>不整脈</td></tr><tr><td>** 過敏症注)</td><td></td><td>そう痒感、発疹</td><td>蕁麻疹、多形紅斑</td></tr><tr><td>消化器</td><td>胃不快感</td><td>嘔気、嘔吐、口渇、便秘、胃重感、胃痛、食欲不振、下痢、嚥下障害</td><td></td></tr><tr><td>** その他</td><td></td><td>鼻閉、浮腫、尿失禁、咽頭灼焼感、全身倦怠感</td><td>味覚異常、女性化乳房、持続勃起症、射精障害、術中虹彩緊張低下症候群、霧視、視力障害、ほてり、熱感、灼熱感</td></tr></table>注）投与を中止すること。</td></tr>
<tr><td>5. 高齢者への投与
高齢者では一般に生理機能が低下しているため、患者の状態を十分に観察しながら投与すること。</td><td>5. 高齢者への投与
高齢者では腎機能が低下していることがあるので、腎機能が低下している場合は 0.1 mg から投与を開始し、経過を十分に観察した後に 0.2 mg に増量すること。0.2 mg で期待する効果が得られない場合にはそれ以上の増量は行わず、他の適切な処置を行うこと。</td></tr>
<tr><td>6. 過量投与
(1) 徴候・症状
外国において、健康成人に本剤を 500 mg まで単回投与した場合及び勃起不全患者に本剤 100 mg を反復投与した場合の副作用は、低用量で認められたものと同様であった。
(2) 処置
過量投与の際の特異的な薬物療法はないが、適切な対症療法を行うこと。なお、腎透析によるクリアランスの促進は期待できない。</td><td>－</td></tr>
</table>

表 1.7-1 同種同効品一覧表 （続き）

一般的名称	タダラフィル	タムスロシン塩酸塩
使用上の注意	7. **適用上の注意** 薬剤交付時：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。［PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。］	6. **適用上の注意** (1) **薬剤交付時**：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。［PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。］ (2) **服用時**： 1) 本剤は噛み砕かずに服用させること。［本剤はタムスロシン塩酸塩の徐放性粒を含有しており、噛み砕いた際に徐放性粒が壊れ、薬物動態が変わる可能性がある。］ 2) 本剤は舌の上にのせ唾液を浸潤させ舌で軽くつぶし、崩壊後唾液のみで服用可能である。 3) 本剤は寝たままの状態では、水なしで服用させないこと。
	8. **その他の注意** (1) 勃起不全治療剤として使用されたタダラフィルの市販後の自発報告において、心筋梗塞、心突然死、心室性不整脈、脳出血、一過性脳虚血発作等の重篤な心血管系障害がタダラフィル投与後に発現している。これらの多くが心血管系のリスクファクターを有している患者であった。多くの事象が、性行為中又は性行為後に認められ、少数例ではあるが、性行為なしにタダラフィル投与後に認められたものもあった。その他は、タダラフィルを投与し性行為後の数時間から数日後に報告されている。これらの症例について、タダラフィル、性行為、本来患者が有していた心血管系障害、これらの要因の組み合わせ又は他の要因に直接関連するかどうかを確定することはできない。なお、性行為を控える必要がある心血管系障害を有する患者には、タダラフィルを勃起不全治療剤として使用することは禁忌とされている。	7. **その他の注意** (1) α_1遮断薬を服用中又は過去に服用経験のある患者において、α_1遮断作用によると考えられる術中虹彩緊張低下症候群（Intraoperative Floppy Iris Syndrome）があらわれるとの報告がある。 (2) 前立腺肥大症の診断・診療については、国内外のガイドライン等の最新の情報を参考にすること。

表 1.7-1 同種同効品一覧表 （続き）

一般的名称	タダラフィル	タムスロシン塩酸塩
使用上の注意	(2)　薬剤との因果関係は明らかではないが、外国において男性勃起不全治療剤として使用されたタダラフィルを含む PDE5 阻害剤投与後に、まれに視力低下や視力喪失の原因となりうる非動脈炎性前部虚血性視神経症（NAION）の発現が報告されている。これらの患者の多くは、NAION の危険因子［年齢（50 歳以上）、糖尿病、高血圧、冠動脈障害、高脂血症、喫煙等］を有していた。 (3)　薬剤との因果関係は明らかではないが、外国において本剤を含む PDE5 阻害剤投与後に、まれに、痙攣発作の発現が報告されている。 (4)　薬剤との因果関係は明らかではないが、外国において本剤を含む PDE5 阻害剤投与後に、まれに、急激な聴力低下又は突発性難聴が報告されている。これらの患者では、耳鳴りやめまいを伴うことがある。 (5)　アルコール飲用時に本剤を投与した外国の臨床薬理試験（本剤 10 mg、20 mg）[注)] において、アルコール血中濃度、本剤の血漿中濃度のいずれも相互に影響を受けなかったが、アルコールを高用量（0.7 g/kg）飲用した被験者において、めまいや起立性低血圧が報告された。 (6) 25 mg/kg/day 以上の用量でタダラフィルをイヌに 3～12 ヵ月間連日経口投与した毒性試験において、精巣重量の低下、精細管上皮の変性、精巣上体の精子数の減少が認められたとの報告がある。ヒトにおける精子形成能に対する影響を検討した外国臨床試験の一部では平均精子濃度の減少が認められたが、精子運動率、精子形態及び生殖ホルモン値はいずれの試験においても変化が認められなかった。 注）本剤の承認された用法・用量は、タダラフィルとして 5 mg である。［「用法・用量」の項参照］	
改訂		2013 年 1 月改訂（第 9 版）

表 1.7-2 同種同効品一覧表

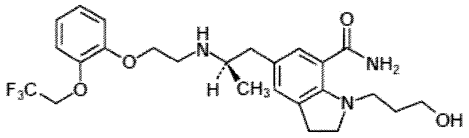
一般的名称	シロドシン
販売名	ユリーフ錠 2 mg ユリーフ錠 4 mg
会社名	キッセイ薬品工業株式会社
承認年月日	2008 年 7 月 25 日
再評価年月日 再審査年月日	－
規制区分	劇薬 処方せん医薬品[注 1)] 注 1）－医師等の処方せんにより使用すること。
化学構造式	
剤型・含量	フィルムコート錠 1 錠中：シロドシン（2 mg） 1 錠中：シロドシン（4 mg）
効能・効果	前立腺肥大症に伴う排尿障害
効能・効果に関連する使用上の注意	本剤は副作用の発現率が高く，特徴的な副作用として射精障害が高頻度に認められているため，本剤の使用にあたっては，本剤のリスクを十分に検討の上，患者に対しては副作用の説明を十分に行った上で使用すること。（「重要な基本的注意」及び「副作用」の項参照）
用法・用量	通常，成人にはシロドシンとして 1 回 4 mg を 1 日 2 回朝夕食後に経口投与する。なお，症状に応じて適宜減量する。
用法・用量に関連する使用上の注意	肝機能障害のある患者ではシロドシンの血漿中濃度が上昇する可能性があり，また，腎機能障害のある患者においては，シロドシンの血漿中濃度が上昇することが報告されているため，患者の状態を観察しながら低用量（1 回 2 mg）から投与を開始するなどを考慮すること。（「薬物動態」の項参照）
使用上の注意	**禁忌（次の患者には投与しないこと）** 本剤の成分に対し過敏症の既往歴のある患者
	1. **慎重投与（次の患者には慎重に投与すること）** (1) 起立性低血圧のある患者［症状が悪化するおそれがある。］ (2) 肝機能障害のある患者［血漿中濃度が上昇するおそれがある。（「用法・用量に関連する使用上の注意」の項参照）］ (3) 腎機能障害のある患者［血漿中濃度が上昇することが報告されている。（「用法・用量に関連する使用上の注意」の項参照）］ (4) ホスホジエステラーゼ 5 阻害作用を有する薬剤を服用している患者（「相互作用」の項参照）
	2. **重要な基本的注意** (1) 射精障害（逆行性射精等）が認められているので，本剤の投与にあたっては射精障害に関する説明を十分に行い，患者の理解を得た上で使用すること。（「副作用」の項参照） (2) 起立性低血圧があらわれることがあるので，体位変換による血圧変化に注意すること。 (3) めまいなどがあらわれることがあるので，高所作業，自動車の運転など危険を伴う作業に従事する場合には注意させること。 (4) 本剤投与開始時に降圧剤投与の有無について問診を行い，降圧剤が投与されている場合には血圧変化に注意し，血圧低下がみられたときには，減量又は中止するなど適切な処置を行うこと。 (5) 本剤による治療は原因療法ではなく，対症療法であることに留意し，本剤投与により期待する効果が得られない場合は，手術療法など，他の適切な処置を考慮すること。

表 1.7-2 同種同効品一覧表 （続き）

<table>
<tr><td>一般的名称</td><td>シロドシン</td></tr>
<tr><td>使用上の注意</td><td>
3. 相互作用
シロドシンは主としてチトクローム P450 3A4（CYP3A4），UDP-グルクロン酸転移酵素，アルコール脱水素酵素及びアルデヒド脱水素酵素により代謝される。（「薬物動態」の項参照）
CYP3A4 活性を強力に阻害する薬剤との併用により，シロドシンの代謝が阻害され，血漿中濃度が上昇する可能性がある。

併用注意（併用に注意すること）
<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>降圧剤</td><td>起立性低血圧があらわれることがあるので，減量するなど注意すること。</td><td>降圧剤服用中の患者は起立時の血圧調節力が低下している場合がある。</td></tr>
<tr><td>アゾール系抗真菌剤
イトラコナゾール等</td><td>強力に CYP3A4 を阻害するケトコナゾール（経口剤：国内未発売）との併用によりシロドシンの血漿中濃度の上昇が認められている。（「薬物動態」の項参照）
アゾール系抗真菌剤との併用により，シロドシンの血漿中濃度が上昇するおそれがあるので，減量するなど注意すること。</td><td>アゾール系抗真菌剤は CYP3A4 を阻害することから，これらの薬剤との併用時には，シロドシンの血漿中濃度が上昇するおそれがある。</td></tr>
<tr><td>ホスホジエステラーゼ 5 阻害作用を有する薬剤
シルデナフィルクエン酸塩，バルデナフィル塩酸塩水和物 等</td><td>併用により症候性低血圧があらわれるとの報告がある。</td><td>本剤はα遮断作用を有するため，併用によりこれらの血管拡張作用による降圧作用を増強するおそれがある。</td></tr>
</table>
4. 副作用
シロドシン（カプセル）承認時までに実施された排尿障害患者対象臨床試験の総症例 873 例中，副作用は 391 例（44.8%）で認められた。その主なものは，射精障害（逆行性射精等）150 例（17.2%），口渇 50 例（5.7%），下痢 35 例（4.0%），軟便 34 例（3.9%），立ちくらみ 31 例（3.6%），鼻閉 29 例（3.3%），めまい 23 例（2.6%），ふらつき 22 例（2.5%），頭痛 19 例（2.2%）などであった。また，臨床検査値の異常変動は，総症例 853 例中 185 例（21.7%）で認められた。その主なものは，トリグリセリド上昇 62 例（7.4%），CRP 上昇 21 例（3.9%），ALT（GPT）上昇 20 例（2.3%），AST（GOT）上昇 19 例（2.2%），γ-GTP 上昇 19 例（2.2%）などであった。

なお，第 III 相二重盲検比較試験では射精障害（逆行性射精等）が 175 例中 39 例（22.3%）で認められた。

(1) 重大な副作用
1) 失神・意識喪失（頻度不明）：血圧低下に伴う一過性の意識喪失等があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止し適切な処置を行うこと。
2) 肝機能障害，黄疸（いずれも頻度不明）：AST（GOT）上昇，ALT（GPT）上昇等を伴う肝機能障害，黄疸があらわれることがあるので，観察を十分に行い，異常が認められた場合には，投与を中止するなど，適切な処置を行うこと。
</td></tr>
</table>

表 1.7-2 同種同効品一覧表 （続き）

一般的名称	シロドシン
使用上の注意	**(2) その他の副作用** 下記の副作用があらわれることがあるので，異常が認められた場合には必要に応じ減量又は投与を中止するなど適切な処置を行うこと。

	頻度不明	5%以上	1～5%未満	0.1～1%未満
泌尿・生殖器		射精障害(逆行性射精等)	インポテンス，尿失禁	
消化器	口内炎	口渇	胃不快感，下痢，軟便，便秘	嘔吐，嘔気，食欲不振，胃痛，腹痛，腹部膨満感，上腹部異和感，下腹部痛，胃潰瘍，胃炎，萎縮性胃炎，胸やけ，胃もたれ感，十二指腸潰瘍，放屁増加，排便回数増加，残便感，肛門不快感
* 精神神経系	しびれ		めまい，立ちくらみ，ふらつき，頭痛	肩こり，頭がボーとする感じ，眠気，性欲減退，頭重感
呼吸器			鼻出血，鼻閉	鼻汁，咳
循環器				心房細動，動悸，頻脈，不整脈，上室性期外収縮，起立性低血圧，血圧低下，血圧上昇
過敏症				発疹，皮疹，湿疹，蕁麻疹，瘙痒感
眼	術中虹彩緊張低下症候群(IFIS)，かすみ目			眼の充血，目のかゆみ，結膜出血
肝臓			AST(GOT)上昇，ALT(GPT)上昇，γ-GTP 上昇，総ビリルビン上昇，Al-P 上昇，LDH 上昇	
腎臓				BUN 上昇，クレアチニン上昇
血液			白血球数減少，赤血球数減少，血色素量減少，ヘマトクリット値減少	白血球数増多，血小板数減少
その他	浮腫，女性化乳房	トリグリセリド上昇	倦怠感，CRP 上昇，総コレステロール上昇，尿糖上昇，尿沈渣上昇	顔のほてり，耳鳴，苦味，胸痛，腰痛，下肢脱力感，発汗，ほてり，気分不良，血清カリウム値上昇，総蛋白低下，前立腺特異抗原増加，尿酸上昇，尿蛋白上昇

5. 高齢者への投与
一般に高齢者では生理機能が低下しており，肝機能又は腎機能が低下している場合は低用量（1 回 2 mg）から投与を開始するなど，患者の状態を十分に観察しながら投与すること。（「用法・用量に関連する使用上の注意」の項参照）

6. 適用上の注意
薬剤交付時：PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。
［PTP シートの誤飲により，硬い鋭角部が食道粘膜へ刺入し，更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することが報告されている。］

7. その他の注意
(1) α_1遮断薬を服用中又は過去に服用経験のある患者において，α_1遮断作用によると考えられる術中虹彩緊張低下症候群（Intraoperative Floppy Iris Syndrome）があらわれるとの報告がある。
(2) マウスでの 104 週間投与試験において，20 mg/kg/日以上の投与群で精嚢腺拡張の頻度の上昇が認められたとの報告がある。
(3) ラットでの受胎能及び着床までの初期胚発生に関する試験において，200 mg/kg/日以上の投与群で精細管に精子細胞の脱落が，600 mg/kg/日投与群で精細管の萎縮・変性，精子生存率及び精子数の減少が認められたとの報告がある。

改訂	2009 年 6 月改訂（第 2 版）

ザルティア錠 5 mg
ザルティア錠 2.5 mg

1.8　添付文書（案）

日本イーライリリー株式会社

目次

1.8 添付文書（案）

1.8.1 添付文書（案）

最新の添付文書を参照すること

LY450190
ザルティア錠

（案）

1.8　添付文書（案）

201x 年 x 月作成

処方せん医薬品
（注意-医師等の処方せんにより使用すること）

前立腺肥大症に伴う排尿障害改善剤
（ホスホジエステラーゼ 5 阻害剤）

日本標準商品分類番号
87 259

ザルティア®錠 2.5 mg①
ザルティア®錠 5 mg②
Zalutia®

タダラフィル錠

	①	②
承認番号		
薬価収載		
販売開始		
国際誕生	2002 年 10 月	2002 年 10 月

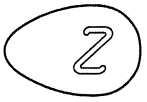
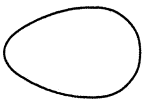
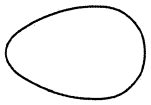
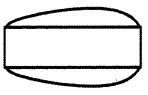
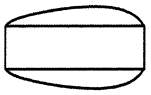
貯　　法：室温保存
使用期限：外箱等に表示

【警告】
1. 本剤と硝酸剤又は一酸化窒素（NO）供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）との併用により降圧作用が増強し、過度に血圧を下降させることがあるので、本剤投与の前に、硝酸剤又は一酸化窒素（NO）供与剤が投与されていないことを十分確認し、本剤投与中及び投与後においても硝酸剤又は一酸化窒素（NO）供与剤が投与されないよう十分注意すること。［「禁忌」の項参照］
2. 死亡例を含む心筋梗塞等の重篤な心血管系等の有害事象が報告されているので、本剤投与の前に、心血管系障害の有無等を十分確認すること。［「禁忌」の項及び「副作用」の項参照］

【禁忌（次の患者には投与しないこと）】
1. **本剤の成分に対し過敏症の既往歴のある患者**
2. **硝酸剤又は一酸化窒素（NO）供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）を投与中の患者［「相互作用」の項参照］**
3. **次に掲げる心血管系障害を有する患者［「その他の注意」の項参照。また、これらの患者に対する使用経験がない。］**
   (1) **不安定狭心症のある患者**
   (2) **心不全（NYHA 分類 III 度以上）のある患者**
   (3) **コントロール不良の不整脈、低血圧（血圧＜90/50 mmHg）又はコントロール不良の高血圧（安静時血圧＞170/100 mmHg）のある患者**
   (4) **心筋梗塞の既往歴が最近 3 ヵ月以内にある患者**
   (5) **脳梗塞・脳出血の既往歴が最近 6 ヵ月以内にある患者**
4. **重度の腎障害のある患者［重度の腎障害のある患者では本剤の血漿中濃度が上昇すること及び使用経験が限られているため。（「薬物動態」の項参照）］**
5. **重度の肝障害のある患者［重度の肝障害のある患者における使用経験がないため。］**

【組成・性状】

販売名	ザルティア錠 2.5 mg	ザルティア錠 5 mg
成分・含量（1 錠中）	タダラフィルとして 2.5 mg	タダラフィルとして 5 mg
添加物	乳糖水和物、結晶セルロース、クロスカルメロースナトリウム、ヒドロキシプロピルセルロース、ステアリン酸マグネシウム、ラウリル硫酸ナトリウム、ヒプロメロース、酸化チタン、トリアセチン、黄色三二酸化鉄、三二酸化鉄、タルク	乳糖水和物、結晶セルロース、クロスカルメロースナトリウム、ヒドロキシプロピルセルロース、ステアリン酸マグネシウム、ラウリル硫酸ナトリウム、ヒプロメロース、酸化チタン、トリアセチン、タルク

性状・剤形		淡橙黄色のフィルムコート錠	白色のフィルムコート錠
外　形	表面		
	裏面		
	側面		
寸法・重量		長径：約 8.7 mm 短径：約 5.4 mm 厚さ：約 3.5 mm 重量：約 0.13 g	長径：約 9.7 mm 短径：約 6.0 mm 厚さ：約 4.0 mm 重量：約 0.18 g
識別コード		2	52

【効能・効果】
前立腺肥大症に伴う排尿障害

＜効能・効果に関連する使用上の注意＞
本剤の適用にあたっては、前立腺肥大症の診断・診療に関する国内外のガイドライン等の最新の情報を参考に、適切な検査により診断を確定すること。

【用法・用量】
通常、成人には 1 日 1 回タダラフィルとして 5 mg を経口投与する。

＜用法・用量に関連する使用上の注意＞
1. 中等度の腎障害のある患者では、本剤の血漿中濃度が上昇する可能性があること及び投与経験が限られていることから、患者の状態を観察しながら 1 日 1 回 2.5 mg から投与を開始するなども考慮すること。［「薬物動態」の項参照］
2. チトクローム P450 3A4（CYP3A4）を強く阻害する薬剤を投与中の患者では、本剤の血漿中濃度が上昇することが認められているので、1 日 1 回 2.5 mg から投与を開始し、患者の状態を観察しながら適宜 5 mg へ増量すること。［「相互作用」の項参照］

【使用上の注意】

1. 慎重投与（次の患者には慎重に投与すること）

(1) α遮断剤を投与中の患者［「相互作用」の項参照］
(2) 軽度・中等度の腎障害のある患者［「薬物動態」の項参照］
(3) 軽度・中等度の肝障害のある患者［投与経験が限られている。］
(4) ホスホジエステラーゼ（PDE）5 阻害剤を投与中の患者［PDE5 阻害剤との併用使用の経験がない。］
(5) 高齢者［「高齢者への投与」の項参照］
(6) 陰茎の構造上欠陥（屈曲、陰茎の線維化、Peyronie 病等）のある患者［本剤の薬理作用により勃起が起こり、その結果陰茎に痛みを引き起こす可能性がある。］
(7) 持続勃起症の素因となり得る疾患（鎌状赤血球性貧血、多発性骨髄腫、白血病等）のある患者
(8) 出血性疾患又は消化性潰瘍のある患者［*in vitro* 試験でニトロプルシドナトリウム（NO 供与剤）の血小板凝集抑制作用を増強することが認められている。出血性疾患又は消化性潰瘍のある患者に対する安全性は確立していない。］
(9) 網膜色素変性症患者［網膜色素変性症の患者には PDE の遺伝的障害を持つ症例が少数認められる。］

2. 重要な基本的注意

(1) 他の PDE5 阻害剤と同様に、本剤は血管拡張作用を有するため一過性の軽度の血圧低下があらわれる場合がある。本剤投与の前に、心血管系障害の有無等を十分確認すること。
(2) α遮断剤と併用する場合は、降圧作用を増強するおそれがあるため、患者背景を考慮して治療上の有益性が危険性を上回る場合にのみ慎重に投与すること。［「相互作用」の項参照］
(3) 4 時間以上の勃起の延長又は持続勃起（6 時間以上持続する痛みを伴う勃起）が外国にてごくまれに報告されている。持続勃起に対する処置を速やかに行わないと陰茎組織の損傷又は勃起機能を永続的に損なうことがあるので、勃起が 4 時間以上持続する症状がみられた場合、直ちに医師の診断を受けるよう指導すること。
(4) 本剤投与後に急激な視力低下又は急激な視力喪失があらわれた場合には、速やかに眼科専門医の診察を受けるよう、患者に指導すること。［「その他の注意」の項参照］
(5) 臨床試験において、めまいや視覚障害が認められているので、高所作業、自動車の運転等危険を伴う機械を操作する際には注意させること。
(6) 本剤投与後に急激な聴力低下又は突発性難聴（耳鳴り、めまいを伴うことがある）があらわれた場合には、速やかに耳鼻科専門医の診察を受けるよう、患者に指導すること。［「副作用」の項及び「その他の注意」の項参照］
(7) 国内において他の前立腺肥大症治療薬と併用した際の臨床効果は確認されていない。
(8) 本剤による治療は原因療法ではなく、対症療法であることに留意し、本剤投与により期待する効果が得られない場合は、手術療法等、他の適切な処置を考慮すること。

3. 相互作用

本剤は主に CYP3A4 により代謝される。

(1) 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
硝酸剤及び NO 供与剤（ニトログリセリン、亜硝酸アミル、硝酸イソソルビド等）	併用により、降圧作用を増強するとの報告がある[1)~3)]。	NO は cGMP の産生を刺激し、一方、本剤は cGMP の分解を抑制することから、両剤の併用により cGMP の増大を介する NO の降圧作用が増強する。

(2) 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A4 阻害剤（イトラコナゾール、クラリスロマイシン、テラプレビル、グレープフルーツジュース等）	強い CYP3A4 阻害作用を有するケトコナゾール（経口剤、国内未発売）との併用により、本剤の AUC 及び C_{max} が 312%及び 22%増加するとの報告がある[4)]。［「薬物動態」の項参照］	CYP3A4 阻害によるクリアランスの減少。
HIV プロテアーゼ阻害剤（リトナビル、インジナビル、サキナビル、ダルナビル等）	リトナビルとの併用により、本剤の AUC が 124%増加するとの報告がある[4)]。［「薬物動態」の項参照］	
CYP3A4 誘導剤（リファンピシン、フェニトイン、フェノバルビタール等）	リファンピシンとの併用により、本剤の AUC 及び C_{max} がそれぞれ 88%及び 46%低下するとの報告がある[5)]。	CYP3A4 誘導によるクリアランスの増加により本剤の血漿中濃度が低下し、本剤の効果が減弱するおそれがある。
α遮断剤（ドキサゾシン、テラゾシン等）	ドキサゾシンとの併用により、立位収縮期血圧及び拡張期血圧は最大それぞれ 9.81 mmHg 及び 5.33 mmHg 下降するとの報告がある[6)]。［「薬物動態」の項参照］また、α遮断剤との併用で失神等の症状を伴う血圧低下を来したとの報告がある。	本剤は血管拡張作用による降圧作用を有するため、併用により降圧作用を増強するおそれがある。
降圧剤（アムロジピン、メトプロロール、エナラプリル、カンデサルタン等）	アンジオテンシンⅡ受容体拮抗剤（単剤又は多剤）との併用により、自由行動下収縮期血圧及び拡張期血圧は最大それぞれ 8 mmHg 及び 4 mmHg 下降するとの報告がある[7)]。	
カルペリチド	併用により降圧作用が増強するおそれがある。	

4. 副作用

承認時までに、日本を含むアジアで実施されたプラセボ対照二重盲検並行群間比較試験（3 試験）において、本剤を投与された総症例 894 例（日本人患者 680 例を含む）中 98 例（11.0%）に副作用が認められた。主な副作用は、消化不良 15 例（1.7%）、頭痛 12 例（1.3%）、CK（CPK）上昇 8 例（0.9%）、筋肉痛 8 例（0.9%）、ほてり 8 例（0.9%）等であった。

(1) 重大な副作用

過敏症（発疹、蕁麻疹、顔面浮腫、剥脱性皮膚炎、Stevens-Johnson 症候群）（頻度不明）：本剤の投与により（男性勃起不全治療剤及び肺動脈性肺高血圧症治療剤としての投与を含む）、発疹、蕁麻疹、顔面浮腫、剥脱性皮膚炎、Stevens-Johnson 症候群等の過敏症が、ごくまれに報告されている。このような症状が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。

(2) その他の副作用

副作用分類	1%以上	1%未満	頻度不明[注 1)]
循環器		動悸、ほてり、潮紅	心筋梗塞、胸痛、心突然死、失神、低血圧
感覚器			眼痛、霧視、結膜充血、網膜動脈閉塞、網膜静脈閉塞、眼瞼腫脹、視野欠損、非動脈炎性前部