トリンテリックス錠 10mg
トリンテリックス錠 20mg

に関する資料

武田薬品工業株式会社

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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 うつ病の病態及び治療

うつ病は、抑うつ気分や興味・喜びの喪失等の症状により、強い苦痛を感じ、日常の生活に支障が出るまでに至った状態をいう。うつ病の中核症状には、抑うつ気分、興味・喜びの喪失のみならず、体重の減少又は増加、食欲の減退又は増加、睡眠障害、精神運動性の焦燥又は制止、疲労感又は気力の減退、無価値観又は罪責感、思考力や集中力の減退及び自殺思考が含まれる。その他に不安症状や様々な身体的症状を訴える患者も多く、さらに妄想や幻覚等の精神病症状が認められることもある[1][2]。

うつ病患者のうち、約 80%は慢性的な経過又は再発を繰り返し、社会機能障害や Quality of life（QOL）低下につながっている[3]。この背景には、記憶・注意・遂行機能といった認知機能障害との関連が想定されており、うつ病の認知機能障害に関する論文の報告件数は年々増加している[4]。認知機能障害の症状（例えば、思考力、集中力又は決断力の低下）はうつ病患者によく認められ、Diagnostic and Statistical Manual of Mental Disorders（DSM）-5 の診断基準に含まれている[1]。遂行機能、処理速度、注意又は学習・記憶等に関連する認知機能の低下は急性期及び寛解期に認められ、これらの機能低下がうつ病の経過及び予後に悪影響を及ぼすと考えられている[5][6]。

うつ病の病因は明らかになっていないが、代表的な仮説として、脳内モノアミン〔5-HT、ドパミン（DA）、ノルアドレナリン（NA）〕の欠乏によりシナプス伝達が低下し、うつ病を発症するとのモノアミン仮説が提唱されている[7]。

うつ病は、1）患者ごとに多様な精神病症状及び身体的症状を呈すること、2）通常、長期の経過をたどり、寛解しても再燃、再発の可能性があること、3）一部の患者は難治性の経過をたどることがあること、4）躁転の可能性があることから、個々の患者に応じた適切な治療を選択することが重要である。

うつ病の治療法には、薬物療法、精神療法、修正型電気痙攣療法、経頭蓋磁気刺激療法及び高照度光療法等の様々な種類がある。「日本うつ病学会治療ガイドライン II. うつ病（DSM－5）／大うつ病性障害 2016」では、うつ病の治療には、まず患者に対する十分な心理教育を基本とし、軽症うつ病の患者では、初診時には支持的精神療法を行い、その後、薬物療法又は認知行動療法を単独又は組み合わせて用いることが検討される。一方、中等度及び重度うつ病の患者では薬物療法が積極的に推奨されている。また、自殺リスクの高い患者又は精神病症状を伴ううつ病等、抗うつ薬による治療が困難な患者に対しては、修正型電気痙攣療法の施行が検討される（図 1.5.1-1）[8]。

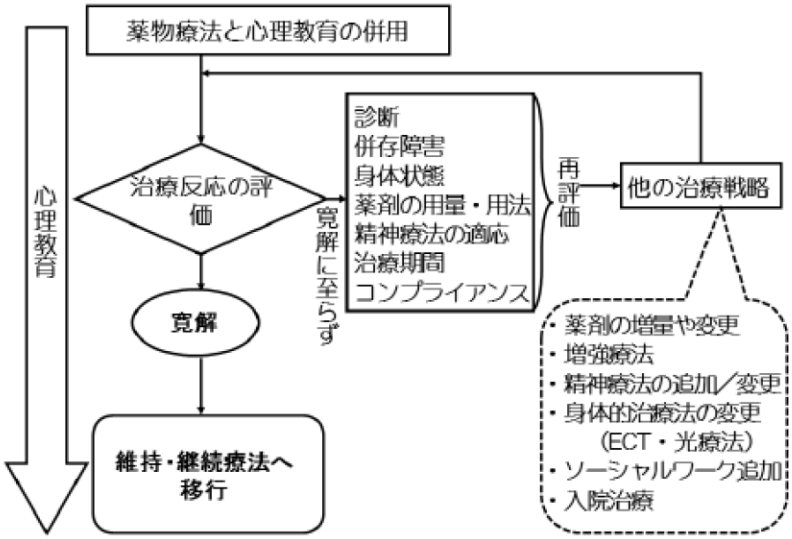

図 1.5.1-1　うつ病治療の手順

（参考文献[8]より抜粋）

うつ病の薬物治療は抑うつ症状から寛解に至る急性期治療、寛解から半年ほど治療を継続して回復に至る持続療法、回復してからも再発予防のために治療を継続する維持療法及び治療を終了する終了期の段階を経る（図 1.5.1-2）[9]。抗うつ薬は通常少量から漸増するが、用量不足若しくは投与期間の不足によるみかけの無反応例又は不完全寛解例があるため、十分な量を十分な期間服用することが重要である。治療期間の目安として、初発例では少なくとも寛解後 4～9 ヵ月、再発例では 2 年以上の期間、急性期と同量で維持すべきとされている[8][10][11]。

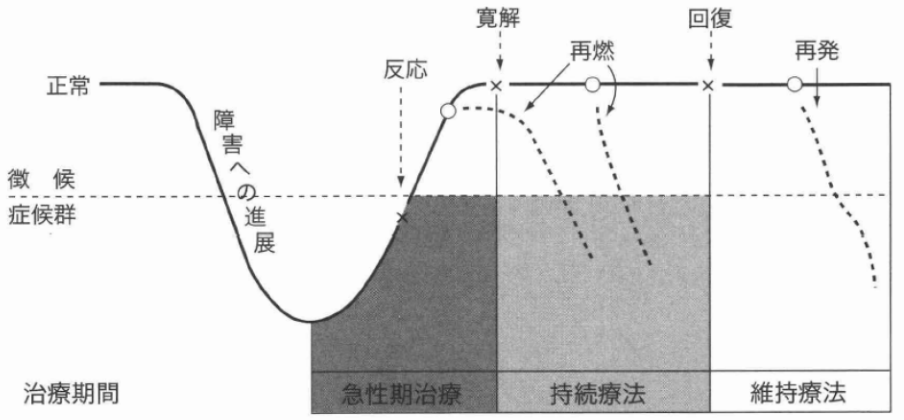

図 1.5.1-2　うつ病治療の各期（急性・持続・維持）における 5 つの転帰

（参考文献[9]より抜粋）

国内で販売されている既存の抗うつ薬は三環系抗うつ薬、四環系抗うつ薬、選択的セロトニン再取り込み阻害薬（SSRI）、セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI）及びノルアドレナリン作動性・特異的セロトニン作動性抗うつ薬（NaSSA）等に分類される。SSRI、SNRI 及び NaSSA は、三環系抗うつ薬に比べて抗コリン作用及び心・循環器系の副作

用の発現頻度が低く、概ね忍容性に優れている。一方、SSRI 及び SNRI を処方する際には、自殺関連行動、アクチベーション症候群又は中止後症状に注意して使用するよう注意喚起されている[12]。四環系抗うつ薬は、鎮静作用による眠気が三環系抗うつ薬と同程度にみられる[13]。

治療には 1 種類の抗うつ薬を使用し、合理性のない多剤併用は行わないことが基本とされている。抗うつ薬の第一選択薬として、中等度のうつ病に対しては SSRI、SNRI 又は NaSSA がよく用いられ、重度のうつ病に対しては全ての抗うつ薬が第一選択薬の候補となり得る。第一選択薬を十分な量かつ十分な期間使用しても反応が得られなかった場合は、抗うつ薬の変更を考慮する。また、第一選択薬を十分な量かつ十分な期間使用しても部分的な反応にとどまる場合は、抗うつ効果増強療法の実施を考慮する[8]。

1.5.2 Lu AA21004 の開発の経緯

Lu AA21004 はセロトニン 3（5-HT_3）、5-HT_7 及び 5-HT_{1D} 受容体アンタゴニスト作用、5-HT_{1B} 受容体部分アゴニスト作用、5-HT_{1A} 受容体アゴニスト作用及びセロトニントランスポーター（SERT）阻害作用を有する。複数の 5-HT 受容体への作用と SERT 阻害作用を介して、5-HT 系、NA 系及び DA 系等複数の神経伝達系において神経伝達物質を調節することが示唆されている。抑うつ症状が消失していく順序として、5-HT 神経伝達系が関与する「不安」、NA 神経伝達系が関与する「意欲」、DA 神経伝達系が関与する「快楽」と報告されている[14]。Lu AA21004 は上記の神経伝達系に関与することが示唆されており、新たな治療選択肢の一つになると考えられる。

また、同じ作用機序の抗うつ薬で治療しても個々の患者により薬剤の反応性が異なることが報告されており、第一選択薬による治療で十分な反応が得られなかった場合、抗うつ薬の変更を考慮することが「日本うつ病学会治療ガイドライン II. うつ病（DSM－5）／大うつ病性障害 2016」で推奨されている[8]。さらに、副作用の発現により服薬を中断する患者は少なくなく、第一選択薬の副作用により投与困難な場合、他の抗うつ薬に切り替えることにより、治療の継続が可能になることもある[15][16]。

これらより、治療の選択肢を増やすことは重要であると考えられ、Lu AA21004 は有効性及び安全性／忍容性の観点から新たな治療選択肢の一つになると考えられる。また、第一選択薬による治療で十分な治療効果が得られなかった患者や投与困難になる副作用が現れた患者に対する切替え治療の選択肢にもなると考えられる。

以上のことから、うつ病・うつ状態の患者に対して Lu AA21004 を開発する意義は大きいと考える。

以下に、Lu AA21004 の品質、非臨床試験及び臨床試験の概要を示した。

1.5.2.1 品質

（1）規格及び試験方法

10 mg 錠及び 20 mg 錠の規格及び試験方法は、実測値、物理的化学的性質、安定性試験の成績及びロット分析結果並びに「新医薬品の規格及び試験方法の設定」（平成 13 年 5 月 1 日付　医薬審発第 568 号）及び「新有効成分含有医薬品のうち製剤の不純物に関するガイドライン」（平成 9 年 6 月 23 日付　薬審第 539 号、平成 15 年 6 月 24 日付　医薬審発第 0624001

号　一部改定、平成 18 年 7 月 3 日付　薬食審査発第 0703004 号　一部改定）に基づき設定した。なお、設定した試験方法については、分析法バリデーションを実施し、採用した規格及び試験方法が妥当であることを確認した。また、試験方法は特に規定しない場合は日局の通則、製剤総則及び一般試験法に準拠した。

（2）安定性試験

10 mg 錠及び 20 mg 錠の安定性試験を「安定性試験ガイドライン」（平成 15 年 6 月 3 日付 医薬審発第 0603001 号）及び「新原薬及び新製剤の光安定性試験ガイドライン」（平成 9 年 5 月 28 日付 薬審第 422 号）に基づき実施した。また、有効期間については「安定性データの評価に関するガイドライン」（平成 15 年 6 月 3 日付 医薬審発第 0603004 号）に基づき設定した。

24 ヵ月までの長期保存試験及び加速試験において、経時的な変化及び変動がほとんど認められなかったことから、「安定性データの評価に関するガイドライン」（平成 15 年 6 月 3 日付 医薬審発第 0603004 号）に基づき、室温保存での有効期間を 36 ヵ月とした。

なお、長期保存試験は [redacted] ヵ月まで試験継続し（20[redacted] 年 [redacted] 月に保存終了予定）、最終的には [redacted] ヵ月間の安定性試験結果をもって、3 年間の有効期間の妥当性を確認する予定である

1.5.2.2 非臨床試験

1.5.2.2.1 薬理試験

効力を裏付ける試験の結果、Lu AA21004 は 2 つの異なる標的クラス（5-HT 受容体及び SERT）が関与したセロトニン再取り込み阻害・セロトニン受容体調節作用を有することが明らかとなった。組換え細胞系の *in vitro* 試験の結果、Lu AA21004 は、h5-HT_3、h5-HT_7、h5-HT_{1D} 受容体アンタゴニスト、h5-HT_{1B} 受容体の部分アゴニスト、h5-HT_{1A} 受容体アゴニスト及び hSERT 阻害剤であることが確認された。ヒトとラット間の受容体親和性の相違により、ラットにおける *in vivo* 薬効においては、ヒトでの薬効に比べて 5-HT_3 及び 5-HT_{1D} 受容体アンタゴニスト作用の影響がやや過大評価され、5-HT_{1A} 受容体アゴニスト作用及び 5-HT_7 受容体アンタゴニスト作用の影響がやや過小評価されている可能性がある。

健常被験者を対象とした結合リガンドを用いたポジトロンエミッショントモグラフィー診断の結果、ヒトに対する投与量 5 mg/日及び 20 mg/日（反復投与）に相当する縫線核における SERT 占有率はそれぞれ約 50%、約 85～90%となった。非臨床試験における Lu AA21004 の薬理学的有効量においては SERT 占拠率は 50%を上回り、*in vivo* 及び *ex vivo* 結合試験の結果、多様な 5-HT 受容体での占有率がこの用量範囲内における Lu AA21004 の作用機序に関与していることが明らかとなった。これらの非臨床所見から、Lu AA21004 は臨床用量において SERT 及び多様な 5-HT 受容体に結合することが示唆される。*in vitro* でのヒトの受容体への結合能の順位（h5-HT_3 > h5-HT_{1A} ≈ h5-HT_7 > h5-HT_{1B} > h5-HT_{1D}）から、用量が増加するに従って、これらの受容体機構が次第に薬効に寄与することが予測される。

in vivo 及び *ex vivo* 結合試験の結果ならびにマイクロダイアリシス法を用いた試験の結果から、5-HT 受容体調節と SERT 阻害の複合作用は、mPFC や VHip など、うつ病に関連する脳内領域において、SERT の低い占有率（40～50%）での細胞外 5-HT の有意な上昇及び SERT の高い占有率での複数の神経伝達物質の上昇（SSRI の作用を超える 5-HT の上昇及び NE、

DA、ACh 及び HA の上昇）に繋がることが示された。さらに、ラット脳波測定による解析では覚醒レベルの増加も報告されている[17]。Lu AA21004 がこのような複数の神経伝達物質の細胞外濃度上昇作用を示す機序の詳細についてはいまだ不明だが、非臨床薬理試験でこれまでに得られている知見から、Lu AA21004 の持つ多様な 5-HT 受容体サブタイプへの作用が寄与している可能性が示唆されている。その中でも特に 5-HT_3 受容体アンタゴニスト作用、5-HT_{1A} 受容体アゴニスト作用、SERT 阻害作用が主な作用点であると考える[18][19]。さらに、上記の段落で検討したとおり、（*in vitro* 親和性強度の順に従い）5-HT_3、5-HT_{1A}、5-HT_7、5-HT_{1B} 及び 5-HT_{1D} 受容体の調節及び SERT 阻害が、Lu AA21004 の臨床用量での薬理作用をもたらすものと予想される。要約すると、これまで述べてきた効力を裏付ける試験の結果から、Lu AA21004 は臨床投与量の範囲内において、特に最高用量を投与した患者において、複数の神経伝達物質の細胞外レベルを引き上げることが強く示唆されている。複数の神経伝達物質系の増強は、Biler 他（2010 年）等の文献報告にあるとおり[20]、臨床における SSRI の増強試験での例と同様に、臨床での有効性を向上させる可能性がある。

高用量 SSRI（SERT 占有率 90%超）と同様に、高用量 Lu AA21004（SERT 占有率 90%超）の投与により、正常ラットにおいて認知機能の改善が認められた。興味深いことに、Lu AA21004 は 0.1 mg/kg 未満という低用量（SERT 占有率 20%未満）においても、5-HT 神経の活動の低いラットにおける認知（記憶力）障害に顕著な効果を示した。SSRI であるエスシタロプラムは本モデルでは作用を示さない。このような記憶能力の改善についての正確な作用機序については不明であるが、5-HT_3 受容体アンタゴニストや 5-HT_{1A} アゴニストを用いた検討から、これら受容体に対する作用が寄与している可能性が考えられた。また、非臨床の電気生理学的検討の結果、5-HT_{1A} 受容体アゴニスト及び 5-HT_3 受容体アンタゴニスト作用により、GABA 作動性介在ニューロンの脱抑制を介して、大脳皮質におけるグルタミン酸作動性ニューロンの発火が増強されることが報告されている[21][22]。これらの所見に関する正確な機序は現在のところ解明されていない。しかし、様々な神経伝達物質レベルへの影響及び大脳皮質におけるグルタミン酸作動性ニューロン発火の増強が、今回観察された認知能力の改善に寄与している可能性がある。

雄性ラットを用いて Lu AA21004 又はフルオキセチンの慢性投与後の性行動を検討した結果、Lu AA21004 は SSRI に比べて、性機能への副作用の可能性が低いことが示唆された。こうした差が生じる原因となった機序については不明である。5-HT_{1A} 受容体のアゴニスト作用及び 5-HT_{1B} 受容体アンタゴニスト作用は雄性ラットの性行動を亢進することが報告されているが[23][24]、5-HT_3 及び 5-HT_7 受容体の役割についてはそれほど研究されていない。Lu AA21004 はラット 5-HT_{1A} 受容体への親和性が低いため、この機序はそれほど重要ではない可能性がある。臨床では、特に SSRI 投与後に引き起こされた性的欲求の低下に対する 5-HT_{1A} 受容体アゴニスト作用の可能性に関する研究が多く実施されている[25][26]。Lu AA21004 の 5-HT_{1A} 受容体への高い親和性を考慮すると、この機序は臨床的な転帰に関係している可能性があるが、その他の 5-HT 受容体サブタイプの調節も関係している可能性がある。

結論として、非臨床試験における Lu AA21004 の薬理学的プロファイルは、新規の作用機序であるセロトニン再取り込み阻害・セロトニン受容体調節作用であり、複数の 5-HT 受容体サブタイプ、特に 5-HT_3 受容体と 5-HT_{1A} 受容体への直接作用、および SERT の阻害作用を

介して 5-HT をはじめとした多様な神経伝達物質（NA、DA、ACh、HA）の放出を調節することに基づいており、SSRI、SNRI、及び NaSSA とは異なっていた。Lu AA21004 の薬理学的プロファイルから、この化合物は臨床における高い忍容性に加え、抗うつ作用を有する可能性が高いことが明らかとなった。また、副次的薬理試験の結果から、抗不安作用、うつ病に伴う認知機能障害に対する改善作用、及び鎮痛作用も持ち合わせている可能性がある。

安全性薬理試験において、Lu AA21004 は臨床での曝露量で良好な忍容性を示し、ヒトの安全性に関連した中枢神経、心血管及び呼吸系の有害事象は認められなかった。さらに、腎・泌尿器及び胃腸管系の検査でも目立った所見はなかった。

1.5.2.2.2 薬物動態試験

ラット及びイヌに経口投与された Lu AA21004 の吸収は速やかであった。また静脈内投与時の血中濃度推移から、Lu AA21004 のこれら動物における全身のクリアランス及び分布容積は高値を示すことがわかった。これら Lu AA21004 の薬物動態学的特徴から Lu AA21004 は初回通過効果が高く、広く組織に分布するために Lu AA21004 及びその由来物質は良好な吸収性を示すものの BA はラットでは 11.2%、イヌでは 36.1%程度と低く算出されたと考えられた。Lu AA21004 はラットにおいて小腸及び大腸から門脈を介して未変化体として吸収され、リンパ経路を介した吸収の寄与は小さいことが示唆された。ラット及びイヌにおける線形性試験では、検討した投与量の範囲で概ね線形動態を示したが、ラット、イヌとも最高用量においてやや投与量比を上回る血中動態を示した。

Lu AA21004 は MDCK 細胞を用いた *in vitro* 試験で中程度又は良好な膜透過性を示した。MDR1 を発現する MDCK 細胞株を使用した *in vitro* 試験において、Lu AA21004 は P-gp の良好な基質ではないと考えられた。また、P-gp の輸送活性に対する Lu AA21004 の IC_{50} 値は 4.14 μmol/L であった。

ラットを用いた[^{14}C]Lu AA21004 の組織分布試験において、放射能は経口投与後速やかに広く組織に分布し、顕著な残留性を示すことなく組織から消失することがわかった。また、Lu AA21004 及びその由来成分はメラニン親和性を有することがわかった。Lu AA21004 の *in vitro* 血漿たん白結合率はマウス、ラット、ウサギ、イヌ及びヒトで高値を示した（98.2%～99.9%）。また、[^{14}C]Lu AA21004 のラット、イヌ及びヒトにおける *in vitro* 血球移行率を調べた結果、いずれの種においても移行率はヘマトクリット値よりも高かった（65.4%～75.5%）。妊娠ラットを用いた試験により、Lu AA21004 及びその由来成分は胎盤を通過して胎児に移行することが示された。

[^{14}C]Lu AA21004 を投与後のマウス血漿中では Lu AA21004 及び Lu AA34443 が、ラット血漿中では Lu AA34443 が、イヌ血漿中では Lu AA34443、M4(b)及び Lu AA21004 が主成分であった。また、経口投与された Lu AA21004 はマウス、ラット、イヌの体内で大部分が代謝され、主に Lu AA34443 として尿、糞中に排泄されることが明らかとなった。

In vitro 及び *in vivo* での Lu AA21004 の代謝試験は、Lu AA21004 が主に酸化及びグルクロン酸抱合によって代謝されることを示した。また *In vitro* 試験から、7 種類の CYP 分子種（CYP2D6、CYP3A4/5、CYP2A6、CYP2C9、CYP2C19、CYP2C8、及び CYP2B6）が Lu AA21004 の代謝に関与すると考えられた。

マウス、ラット及びイヌ並びにヒトに[^{14}C]Lu AA21004 を単回経口投与又は Lu AA21004 を反復経口投与したときの代謝物の全身曝露量を比較すると、安全性評価で用いた少なくとも 1 つの動物種における代謝物の曝露量は、臨床最大用量付近での曝露量以上又は同程度であったことが示された。

Lu AA21004 及びその代謝物 Lu AA34443 は、ヒト CYP 分子種に対して全く又はわずかな阻害作用しか示さなかったが、代謝物 Lu AA39835 は CYP2C19 活性を阻害し Ki 値は 1 µmol/L 未満であった。ヒト肝細胞を用いて Lu AA21004 及び Lu AA34443 の誘導作用を検討した結果、CYP1A2、CYP2A6、CYP2B6、CYP2C8、CYP2C9、CYP2C19 及び CYP3A4/5 の酵素活性あるいは mRNA 量に対してほとんど影響を与えなかった。

[^{14}C]Lu AA21004 及びその由来成分は、マウス、ラット及びイヌにおいて経口投与後、糞中及び尿中の両方に排泄され、糞中排泄が尿排泄を上回った。これら動物における放射能の排泄はほぼ定量的であり、体内残留性は示さなかった。また、[^{14}C]Lu AA21004 及びその由来成分の一部は授乳ラットにおいて乳汁に移行し、乳汁を介して排泄されることが確認された。

Lu AA21004 及びその代謝物 Lu AA34443 の BCRP、BSEP、OATP1B1、OATP1B3、OCT1、OCT2、MATE1、MATE2-K、OAT1 及び OAT3 に対する阻害効果を検討した結果、Lu AA21004 は OCT1、OCT2、MATE1 及び MATE2-K の輸送活性を阻害し、OCT1、OCT2、MATE1 及び MATE2-K に対する IC_{50} 値はそれぞれ 1.93、12.3、21.7 及び 43.7 µmol/L と算出された。また、Lu AA34443 は OCT1 及び MATE1 の輸送活性を阻害し、OCT1 及び MATE1 に対する IC_{50} 値はそれぞれ 9.18 及び 18.5 µmol/L と算出された。その他のトランスポーターに対して Lu AA21004 及び Lu AA3444 は阻害作用を示さなかった。

以上、薬物動態試験において実施した動物種の全身循環での代謝物分析の結果から、毒性試験でのこれら動物種の全身暴露はヒトで検出された Lu AA21004 及びその代謝物の曝露量を上回ること、又は同程度であることが確認された。さらにこれら動物種を用いた薬物動態試験の成績から、これら動物種における Lu AA21004 の吸収、分布、代謝、排泄が考察可能であることが示された。

1.5.2.2.3 毒性試験

単回経口投与毒性試験では、マウス及びラットの概略の致死量はそれぞれ 500 mg/kg 及び> 500 mg/kg、最大耐量（MTD）はそれぞれ 300 mg/kg 及び 500 mg/kg であり、これらの用量における主な所見は、外的刺激に対する過敏性、呼吸促迫、鼻周囲汚染（褐色）であった。

反復投与毒性試験として、マウス、ラット及びイヌを用いてそれぞれ最長 13、26 及び 52 週間の反復投与毒性試験を実施した。反復投与毒性試験で認められた主な所見は、Lu AA21004 の中枢神経系への作用に関連すると考えられるラット及びイヌの流涎並びにイヌの散瞳、また、ラット及びマウスの肝臓及びラットの腎臓における代謝物の析出により生じた結晶性物質による閉塞性変化とそれに関連した変化であった。各動物における最長の反復投与毒性試験であるマウス 13 週、ラット 26 週及びイヌ 52 週間毒性試験における無毒性量は、それぞれ 50 mg/kg/日, 10 mg/kg BID 及び 7.5 mg/kg/日であった。

遺伝毒性試験として、細菌を用いる復帰変異原性試験、ヒト末梢血リンパ球を用いる *in vitro* 染色体異常試験及びラットを用いる *in vivo* 小核試験を実施し、Lu AA21004 は遺伝毒性を示さなかった。

がん原性試験では、雌雄ラットと雄のマウスで肝細胞腺腫の発生率増加が認められた。発生率の増加がみられた用量では、肝胆道系における結晶析出及び二次的な炎症性変化がみられ、持続的な肝臓障害が生じていたものと考えられた。臨床用量でヒトの肝胆道系に結晶析出とその二次的な変化が起こる可能性は低いと考えられることから、臨床での発がん性を示唆する所見はないと判断した。

ラットの受胎能及び着床までの初期胚･胎児発生に関する試験では､ラットに 60 mg/kg BID まで投与した結果、受胎能、交配行動、生殖器官又は精子形態及び運動性に影響は認められなかった。胚・胎児発生試験では、ラットに 80 mg/kg BID まで及びウサギに 15 mg/kg BID まで投与した結果、妊娠パラメータへの影響や奇形の誘発、胎児生存率への影響はみられなかったが、本薬投与に関連した胎児の体重低値及び骨化遅延は認められた。ラットの出生前及び出生後の発育並びに母体の機能に関する試験では、最高用量 60 mg/kg BID まで投与した結果、母体毒性が認められなかった用量においても、出生児ラットの死亡率の上昇、体重増加の抑制、開眼の遅延が認められた。このことから、本薬投与により出生前後の発育への影響が生じる可能性は排除できないと考えられた。

幼若ラットの毒性試験では、生後 21 日の幼若ラットに 40 mg/kg BID まで 10 週間投与した結果、成熟ラットを用いた反復投与毒性試験及び生殖発生毒性試験の結果と質的に異なる新規所見は認められず、無毒性量は 20 mg/kg BID であった。

一連の毒性試験における無毒性量又は非発がん量における曝露量は、出生児ラットの発育に関する影響及びラットがん原性試験における雄ラット腸間膜リンパ節における良性血管腫の発現頻度の増加を除いて、最大臨床用量（20 mg/日）での曝露量を上回っていた。

1.5.2.3 臨床試験

（1）臨床試験開発計画

Lu AA21004 の承認申請においては、国際共同試験（CCT-002 試験）を含め、当社が実施した日本人を対象とした国内臨床試験（CPH-001、CPH-002、CPH-003、CPH-004、Vortioxetine-1001、CCT-003、CCT-004 及び OCT-001 試験）を評価資料とし、H. Lundbeck A/S 又は Takeda Global Research & Development Center, Inc.によって実施された海外試験を参考資料とした。本パッケージに含まれる試験は、臨床薬理試験 29 試験、プラセボ対照二重盲検比較試験 13 試験（高齢者を対象とした 1 試験を含む）、短期実薬対照試験 2 試験、長期プラセボ対照再燃予防試験 1 試験及び非盲検、長期継続試験 6 試験である。

（2）有効性について

Lu AA21004 の有効性評価は、大うつ病性障害患者を対象に実施した日本を含む第 2/3 相国際共同試験 1 試験（CCT-002 試験）及び国内第 3 相試験 3 試験（CCT-003､CCT-004 及び OCT-001 試験）の計 4 試験を評価資料とし、検討した。評価資料の試験のうち、短期投与の有効性は、短期投与試験（CCT-002、CCT-003 及び CCT-004 試験）の結果に基づき評価した。長期投与の有効性は、CCT-003 試験の継続投与試験である OCT-001 試験の結果に基づき評価した。

CCT-004 試験を実施した結果、主要評価項目であるベースラインから投与 8 週時点までの MADRS 合計スコアの変化量について、プラセボ群との最小二乗平均値の差は、Lu AA21004 10 mg 群及び 20 mg 群のいずれの群でも統計学的に有意な差が認められ、この変化量が、-2 より大きいことから、臨床的に意義のある抑うつ症状の改善がみられたことを示している [27]。

（3）安全性について

Lu AA21004 の安全性評価は、健康成人又は健康高齢者を対象に実施した国内第 1 相試験 5 試験（CPH-001、CPH-002、CPH-003、CPH-004 試験及び Vortioxetine-1001 試験）並びに大うつ病性障害患者を対象に実施した日本を含む第 2/3 相国際共同試験 1 試験（CCT-002 試験）、国内第 3 相試験 3 試験（CCT-003、CCT-004 及び OCT-001 試験）の計 9 試験を評価資料とし、検討した。短期投与の安全性は、短期投与試験（CCT-002、CCT-003 及び CCT-004 試験）の各試験結果に加え、試験デザイン及び投与期間が類似していることから、短期投与試験 3 試験を併合解析（「短期投与試験併合」）し、評価した。長期投与の安全性は、CCT-003 試験の継続投与試験である OCT-001 試験結果に基づき評価した。

プラセボ対照二重盲検比較試験である CCT-003 試験における短期投与時と比較し、OCT-001 試験の長期継続投与時に顕著に発現率が高くなる有害事象はなく、投与期間に伴って発現率の高くなる有害事象もみられなかったことから、Lu AA21004 の安全性は問題ないと考えられる。

国内外における開発の経緯について、表 1.5.2-1 に示した。

表 1.5.2-1　開発の経緯

試験項目			[redacted]
品質	製剤及び処方		
	製剤開発の経緯		
	製造	製剤	
	管理（又は規格及び試験方法）	製剤	
	標準品又は標準物質	製剤	
	容器及び施栓系	製剤	
	安定性試験（現在実施中）	製剤	
薬理	効力を裏付ける試験		
	副次的薬理試験		
	安全性薬理試験		
動態	薬物動態試験		
毒性	単回・反復投与毒性試験		
	遺伝毒性試験		
	がん原性試験		
	生殖発生毒性試験		
	その他の毒性試験		

表 1.5.2-1　開発の経緯（続き）

	実施地域	試験項目（試験番号）		[redacted]
臨床(評価)	国内	第1相	単回及び反復投与試験（CPH-001 試験）	
		医薬品[redacted]相談		
		第1相	反復投与試験（CPH-002 試験）	
			高齢男女対象単回投与試験（CPH-003 試験）	
		医薬品[redacted]相談		
		第1相	食事の影響検討試験（CPH-004 試験）	
		第2/3相	用量設定試験（CCT-002 試験）	
		第3相	二重盲検比較試験（CCT-003 試験）	
			長期継続投与試験（OCT-001 試験）	
		医薬品[redacted]相談		
		第3相	二重盲検比較試験（CCT-004 試験）	

1.5.3 予定する効能又は効果、用法及び用量

品質、非臨床試験及び臨床試験により、Lu AA21004 の有効性・安全性が確認されたことから、表 1.5.3-1 に示す効能又は効果、用法及び用量にて医薬品製造販売承認申請を行うこととした。

表 1.5.3-1　効能又は効果、用法及び用量

販売名	トリンテリックス錠 10 mg、トリンテリックス錠 20 mg
申請区分	医療用医薬品（1）新有効成分含有医薬品
適応症（効能又は効果）	うつ病・うつ状態
用法及び用量	通常、成人にはボルチオキセチンとして 10 mg を 1 日 1 回経口投与する。なお、患者の状態により 1 日 20 mg を超えない範囲で適宜増減するが、増量は 1 週間以上の間隔をあけて行うこと。

1.5.4 治験相談等の経緯

本剤の開発に際し、以下の対面助言を行った。

（1）医薬品[redacted]相談（受付日・番号：平成[redacted]年[redacted]月[redacted]日・[redacted]）

[redacted]について、[redacted]とすることに合意が得られ、[redacted]との助言を得た。[redacted]に関して、[redacted]を検討することについて助言を得た。

（2）医薬品[redacted]相談（受付日・番号：平成[redacted]年[redacted]月[redacted]日・[redacted]）

[redacted]について再度検討する必要があるとの助言から、[redacted]とする[redacted]した。[redacted]については、[redacted]とすることで合意を得た。

（3）医薬品[redacted]相談（受付日・番号：平成[redacted]年[redacted]月[redacted]日・[redacted]）

[redacted]について助言を得た。また、[redacted]について、[redacted]との見解を得た。

1.5.5 本剤の特徴及び有用性

大うつ病性障害患者を対象とした CCT-004 試験では、主要評価項目である MADRS 合計スコアのベースラインからの変化量について、Lu AA21004 群とプラセボ群との間で統計学的に有意な差がみられ、臨床的に意義のある抑うつ症状の改善がみられた。さらに、投与開始

時から有効用量での治療が可能である。また、OCT-001 試験では、長期投与時においても抗うつ効果は維持されることが確認された。

これらの臨床試験成績及びセロトニン再取り込み阻害・セロトニン受容体調節作用を有する抗うつ薬であることから、Lu AA21004 はうつ病治療における新たな選択肢となることが期待できる。

安全性については、国内で実施した臨床試験において安全性に特に懸念すべき問題はみられず、忍容性は良好であったが、Lu AA21004 の作用機序並びに非臨床試験成績及び海外製造販売後の報告に基づき、以下を医薬品リスク管理計画書において安全性検討事項の重要な特定されたリスク及び重要な潜在的リスクとし、製造販売後も引き続き情報収集を行い、添付文書等において注意喚起することでリスクを最小化することができると考える。

重要な特定されたリスク
・セロトニン症候群
・痙攣
・SIADH・低ナトリウム血症

重要な潜在的リスク
・自殺念慮・自殺行動
・出血
・妊婦への投与による児への影響（PPHN 等）

以上のことから、Lu AA21004 のベネフィットはリスクを上回り、Lu AA21004 をうつ病治療の選択肢の一つとして、医療現場に提供することは臨床的に意義があると考える。

これまでに得られた臨床試験成績を踏まえ、Lu AA21004 のベネフィットを以下に示した。

（1）うつ病に対して優れた効果を示した

STAR*D 研究で示されたように複数の薬物治療を実施したにもかかわらず寛解に至らない患者や既存の抗うつ薬では十分な抗うつ効果を得られない患者がいることから、新しい作用機序の抗うつ薬が望まれている[2][28]。大うつ病性障害患者を対象にプラセボ対照二重盲検比較試験（CCT-004 試験）を実施した結果、主要評価項目であるベースラインから投与 8 週時点までの MADRS 合計スコアの変化量について、プラセボ群との最小二乗平均値の差は、Lu AA21004 10 mg 群及び 20 mg 群のいずれの群でも統計学的に有意な差が認められ、この変化量が、-2 より大きいことから、臨床的に意義のある抑うつ症状の改善がみられたことを示している[27]。

また、MADRS 反応率（MADRS 合計スコアがベースラインから 50%以上減少した被験者の割合）、MADRS 寛解率（MADRS 合計スコアが 10 以下に減少した被験者の割合）及び HAM-D17 合計スコアのベースラインからの変化量でも主要評価項目と同様にいずれの群でもプラセボ群に対して統計学的に有意であった。

加えて、仕事／学業、社会生活及び家族内のコミュニケーションや役割といった総合的機能領域における障害の程度を評価するために、SDS による評価を実施した。SDS 合計スコア

のベースラインからの変化量に関して、Lu AA21004 10 mg 群及び 20 mg 群はプラセボ群に対して統計学的に有意な差がみられた。

以上の結果から、Lu AA21004 は、複数の 5-HT 受容体への作用と SERT 阻害作用を有する新規の作用機序の抗うつ薬であり、SSRI、SNRI 又は NaSSA とは異なる作用機序を有し、うつ病及びうつ病に伴う総合的機能障害に対する有効性を示していることから、うつ病治療の新たな選択肢となり得ると考えられる。

（2）長期投与において、抗うつ効果の維持が期待される

うつ病の治療は抑うつ症状から寛解に至る急性期治療、寛解から半年ほど治療を継続して回復に至る持続療法、回復してからも再発予防のために治療を継続する維持療法、治療を終了する終了期の段階を経る[9]。長期投与試験（OCT-001 試験）において、MADRS 合計スコアのベースライン（OCT-001 試験の開始時）からの変化量（平均値）は、投与期間を通して経時的な低下がみられた。

再燃予防試験（11985A 試験）において、二重盲検投与期間の投与 24 週以内に再燃した被験者の割合を検討した結果、Lu AA21004 群はプラセボ群に対して、再燃リスクが有意に低下し、プラセボ群における再燃リスクは、Lu AA21004 群に比べて約 2 倍であった。

以上の結果から、Lu AA21004 は、うつ病に対して長期の有効性が期待され、急性期治療後に継続して治療を行うことができる。

（3）長期投与において良好な安全性を示した

うつ病の治療では、長期にわたって、抗うつ効果があり、安全に使用できる薬剤が求められている。

安全性に関して、プラセボ対照二重盲検比較試験である CCT-003 試験における短期投与時と比較し、OCT-001 試験の長期継続投与時に顕著に発現率が高くなる有害事象はなく、投与期間に伴って発現率の高くなる有害事象もみられなかったことから、Lu AA21004 の安全性は問題ないと考えられる。

以上の結果から、Lu AA21004 は、長期投与における安全性が期待され、うつ病の長期にわたる治療を行うことができる。

（4）漸増が不要であり、有効用量から開始できる

既存の抗うつ薬においては、副作用軽減のため、有効用量に至らない用量から投与を開始し、有効用量まで漸増が必要となる薬剤が存在する。

プラセボ対照二重盲検比較試験（CCT-004 試験）の結果、主要評価項目である投与 8 週時点における MADRS 合計スコアのベースラインからの変化量の主解析（MMRM）では、Lu AA21004 10 及び 20 mg 群とプラセボ群との間に統計学的に有意な差が認められ、このうちの最小有効用量である Lu AA21004 10 mg 群に関して、安全性に問題はみられず、忍容性は良好であった。

以上の結果から、Lu AA21004 は、漸増が不要であり、有効用量からの投与開始が可能である。

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目次

表

1.6 外国における使用状況等に関する資料

（1）外国での許可及び使用状況

Lu AA21004 は米国及び欧州を含む世界 83 ヵ国で承認されている（2019 年 4 月現在）。米国／欧州における Lu AA21004 の承認取得状況を表 1.6-1 に示す。また、米国／欧州の labeling 及び企業中核データシートを次頁以降に添付した。

表 1.6-1　米国／欧州における Lu AA21004 の承認取得状況

国名	販売名	承認年月日	剤型	含量	効能・効果 用法・用量
米国	TRINTELLIX	2013 年 9 月 30 日	フィルムコーティング錠	5 mg 10 mg 20 mg	効能・効果 トリンテリックスは、成人の大うつ病性障害の治療に用いられる。 用法・用量 · 推奨開始用量は 10 mg 1 日 1 回であり、食事の影響なく服用できる。 · 患者が忍容性に応じて、20 mg 1 日 1 回に増量すること。 · 高用量の忍容性に懸念がある場合、5 mg 1 日 1 回投与を考慮する。 · トリンテリックスはすぐに中止することができるが、15 又は 20 mg 1 日 1 回服用している患者では、服用中止前 1 週間は、可能ならば 10 mg 1 日 1 回投与を推奨する。 · CYP2D6 の活性が欠損していることが判明している患者（poor metabolizers）では、最大推奨用量は 10 mg 1 日 1 回である。
欧州	Brintellix	2013 年 12 月 18 日	フィルムコーティング錠	5 mg 10 mg 15 mg 20 mg	4.1 効能・効果 ブリンテリックスは成人の大うつ病性障害の治療に用いられる。 4.2 用法・用量 <u>用量</u> 65 歳未満の成人患者において、ブリンテリックスの開始及び推奨用量はボルチオキセチンとして、10 mg 1 日 1 回である。患者の反応性に応じて最大 20 mg 1 日 1 回まで増量、また、5 mg 1 日 1 回に減量可能である。うつ症状が消失した後、少なくとも 6 ヵ月間治療を維持することが推奨される。 <u>投与の中止</u> ボルチオキセチンの投与を受けた患者は、減量することなくすぐに中止することができる。 <u>特殊な集団</u> [1)] ・高齢者：65 歳以上の患者における開始用量はいつもボルチオキセチンとして、5 mg 1 日 1 回にすべきである。臨床データが限られているため、65 歳以上の患者にボルチオキセチン 10 mg 1 日 1回を上回る用量で投与する場合には注意が必要である。 ・チトクローム P450 阻害剤：個々の患者の反応に応じて、ボルチオキセチンの投与に強力な CYP2D6 阻害剤（ブプロピオン、キニジン、フルオキセチン、パロキセチン等）を追加する場合、低用量のボルチオキセチンを投与することを考慮する。 <u>投与方法</u> ブリンテリックスは経口投与用である。フィルムコーティング錠は食事の影響なく服用できる。

1)　低用量投与の必要性が設定されている記載を抜粋した。

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

TRINTELLIX (vortioxetine) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **TRINTELLIX has not been evaluated for use in pediatric patients (8.4).**

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 10/2018

----------INDICATIONS AND USAGE----------
TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults (1, 14).

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 10 mg administered orally once daily without regard to meals (2.1).
- The dose should then be increased to 20 mg/day, as tolerated (2.1).
- Consider 5 mg/day for patients who do not tolerate higher doses (2.1).
- TRINTELLIX can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible (2.3).
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers (2.6).

----------DOSAGE FORMS AND STRENGTHS----------
TRINTELLIX is available as 5 mg, 10 mg and 20 mg immediate release tablets (3).

----------CONTRAINDICATIONS----------
- Hypersensitivity to vortioxetine or any components of the TRINTELLIX formulation (4).
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue (4).

----------WARNINGS AND PRECAUTIONS----------
- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with TRINTELLIX, both when taken alone, but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue TRINTELLIX and initiate supportive treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.3).
- Activation of Mania/Hypomania can occur with antidepressant treatment. Screen patients for bipolar disorder (5.4).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.5).
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong inhibitors of CYP2D6: Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is coadministered (2.6, 7.3).
- Strong CYP Inducers: Consider increasing TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose (2.7, 7.3).

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Third trimester use may increase risk for persistent pulmonary hypertension and withdrawal in the newborn (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

TRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended starting dose is 10 mg administered orally once daily without regard to meals. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses *[see Clinical Studies (14)]*.

2.2 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression should be followed by several months or longer of sustained pharmacologic therapy. A maintenance study of TRINTELLIX demonstrated that TRINTELLIX decreased the risk of recurrence of depressive episodes compared to placebo.

2.3 Discontinuing Treatment

Although TRINTELLIX can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of TRINTELLIX 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of TRINTELLIX 15 mg/day or 20 mg/day *[see Adverse Reactions (6)]*.

2.4 Switching a Patient to or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with TRINTELLIX to avoid the risk of Serotonin Syndrome *[see Warnings and Precautions (5.2)]*. Conversely, at least 21 days should be allowed after stopping TRINTELLIX before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)]*.

2.5 Use of TRINTELLIX with Other MAOIs such as Linezolid or Methylene Blue

Do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)]*.

In some cases, a patient already receiving TRINTELLIX therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, TRINTELLIX should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 21 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with TRINTELLIX may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)]*.

The risk of administering methylene blue by nonintravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with TRINTELLIX is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors

The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued *[see Drug Interactions (7.3)]*.

2.7 Use of TRINTELLIX in Patients Taking Strong CYP Inducers

Consider increasing the dose of TRINTELLIX when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of TRINTELLIX should be reduced to the original level within 14 days, when the inducer is discontinued *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRINTELLIX is available as immediate-release, film-coated tablets in the following strengths:

- 5 mg: pink, almond shaped biconvex film coated tablet, debossed with “5” on one side and “TL” on the other side
- 10 mg: yellow, almond shaped biconvex film coated tablet, debossed with “10” on one side and “TL” on the other side
- 20 mg: red, almond shaped biconvex film coated tablet, debossed with “20” on one side and “TL” on the other side

4 CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with TRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of TRINTELLIX within 14 days of stopping an MAOI

intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.

Starting TRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	**Increases Compared to Placebo**
<18	14 additional cases
18 - 24	5 additional cases
Age Range	**Decreases Compared to Placebo**
25 - 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies

in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRINTELLIX is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including TRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of TRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. TRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking TRINTELLIX. TRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications (4), Dosage and Administration (2.4)]*.

If concomitant use of TRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions (7.2)]*.

5.4 Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with TRINTELLIX in premarketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use TRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.5 Angle Closure Glaucoma

Angle Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.6 Hyponatremia

Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with TRINTELLIX in a premarketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of TRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which

can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications (4)]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.3)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Angle Closure Glaucoma *[see Warnings and Precautions (5.5)]*
- Hyponatremia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Studies 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 studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

TRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in premarketing clinical studies; 2616 of those patients were exposed to TRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to TRINTELLIX in a 24 to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12 month open-label studies. A total of 2586 patients were exposed to at least one dose of TRINTELLIX in open-label studies, 1727 were exposed to TRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in MDD patients treated with TRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any TRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2. Common Adverse Reactions Occurring in ≥2% of Patients Treated with any TRINTELLIX Dose and at Least 2% Greater than the Incidence in Placebo-treated Patients

System Organ Class Preferred Term	TRINTELLIX 5 mg/day	TRINTELLIX 10 mg/day	TRINTELLIX 15 mg/day	TRINTELLIX 20 mg/day	Placebo
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

* includes pruritus generalized

Nausea

Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was two weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of TRINTELLIX treatment with 15 to 20% of patients experiencing nausea after one to two days of treatment. Approximately 10% of patients taking TRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment. In addition to the data from the MDD studies mentioned below, TRINTELLIX has been prospectively assessed for its effects in MDD patients with existing TESD induced by prior SSRI treatment and in healthy adults with normal sexual function at baseline *[see Clinical Studies (14)]*.

Voluntarily Reported Adverse Reactions of Sexual Dysfunction

In the MDD 6 to 8 week controlled trials of TRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their self-reported ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed TESD when treated with TRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	**TRINTELLIX 10 mg/day** N=94:86†	**TRINTELLIX 15 mg/day** N=57:67†	**TRINTELLIX 20 mg/day** N=67:59†	**Placebo** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

* Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

Adverse Reactions Following Abrupt Discontinuation of TRINTELLIX Treatment

Discontinuation symptoms have been prospectively evaluated in patients taking TRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of TRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests

TRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of TRINTELLIX *[see Warnings and Precautions (5.6)]*. In the six month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12 week, open-label phase, there were no clinically important changes in lab test parameters between TRINTELLIX and placebo-treated patients.

Weight

TRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the six month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during

the initial 12 week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients.

Vital Signs
TRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo

Gastrointestinal disorders — dyspepsia

Nervous system disorders — dysgeusia

Vascular disorders — flushing

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of TRINTELLIX. 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.

Metabolic disorders — weight gain

Nervous system disorders — seizure

Skin and subcutaneous tissue disorders — rash, generalized rash

Gastrointestinal System — acute pancreatitis

7 DRUG INTERACTIONS

7.1 CNS Active Agents

Monoamine Oxidase Inhibitors
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2)]*.

Serotonergic Drugs
Based on the mechanism of action of TRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when TRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if TRINTELLIX is coadministered with other serotonergic drugs. Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions (5.2)]*.

Other CNS Active Agents
No clinically relevant effect was observed on steady-state lithium exposure following coadministration with multiple daily doses of TRINTELLIX. Multiple doses of TRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg).

Details on the potential pharmacokinetic interactions between TRINTELLIX and bupropion can be found in Section 7.3.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

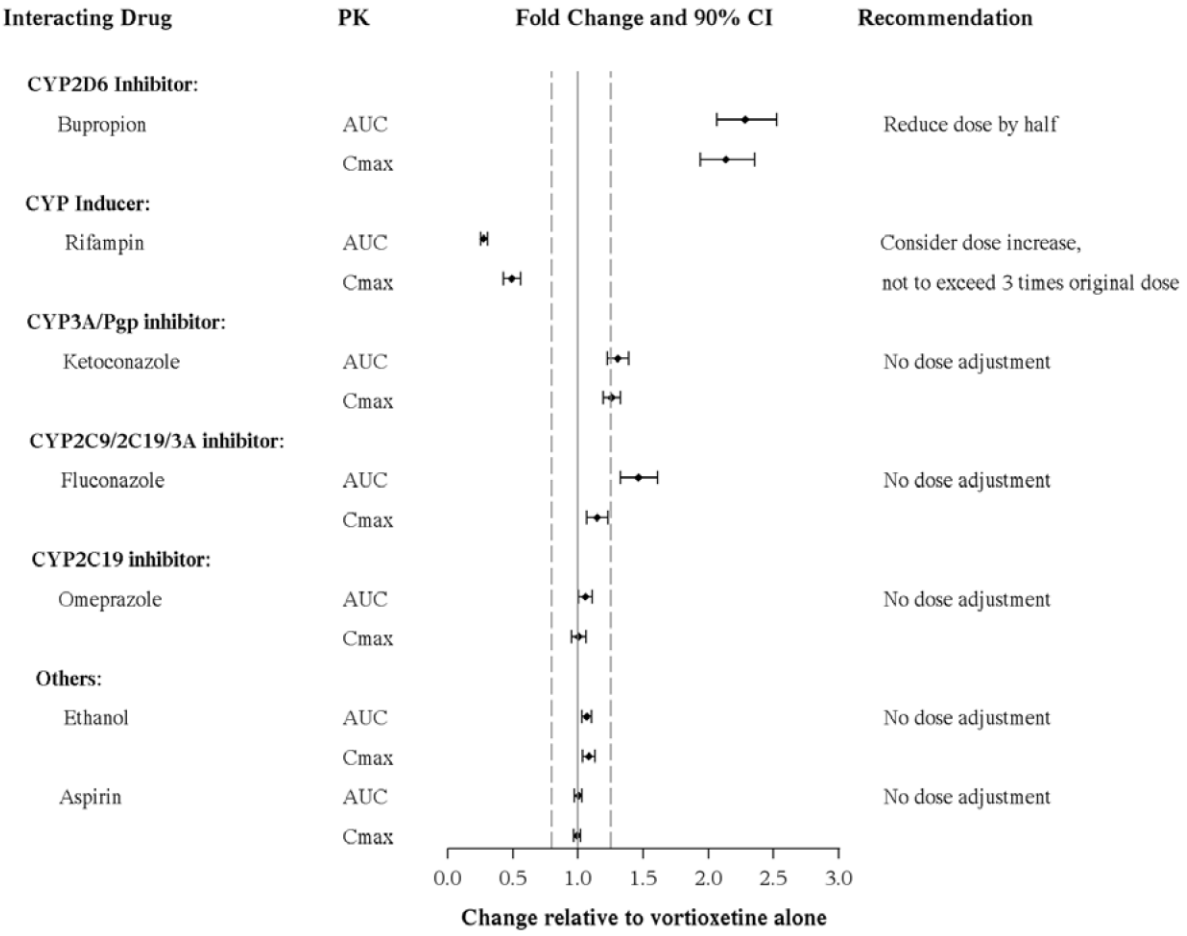
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of TRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions (7.4)]*. Coadministration of aspirin 150 mg/day with multiple daily doses of TRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions (7.4)]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions (5.3)]*.

7.3 Potential for Other Drugs to Affect TRINTELLIX

Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose *[see Dosage and Administration (2.5, 2.6)] (Figure 1)*.

Figure 1. Impact of Other Drugs on Vortioxetine PK



7.4 Potential for TRINTELLIX to Affect Other Drugs

No dose adjustment for the comedications is needed when TRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine, caffeine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinide), CYP2C9 (e.g., S-warfarin, tolbutamide), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine, dextromethorphan), CYP3A4/5 (e.g., budesonide, midazolam), P-gp (e.g., digoxin), BCRP (e.g., methotrexate), OATP1B1/3 (e.g., rosuvastatin) and OCT2 (e.g., metformin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

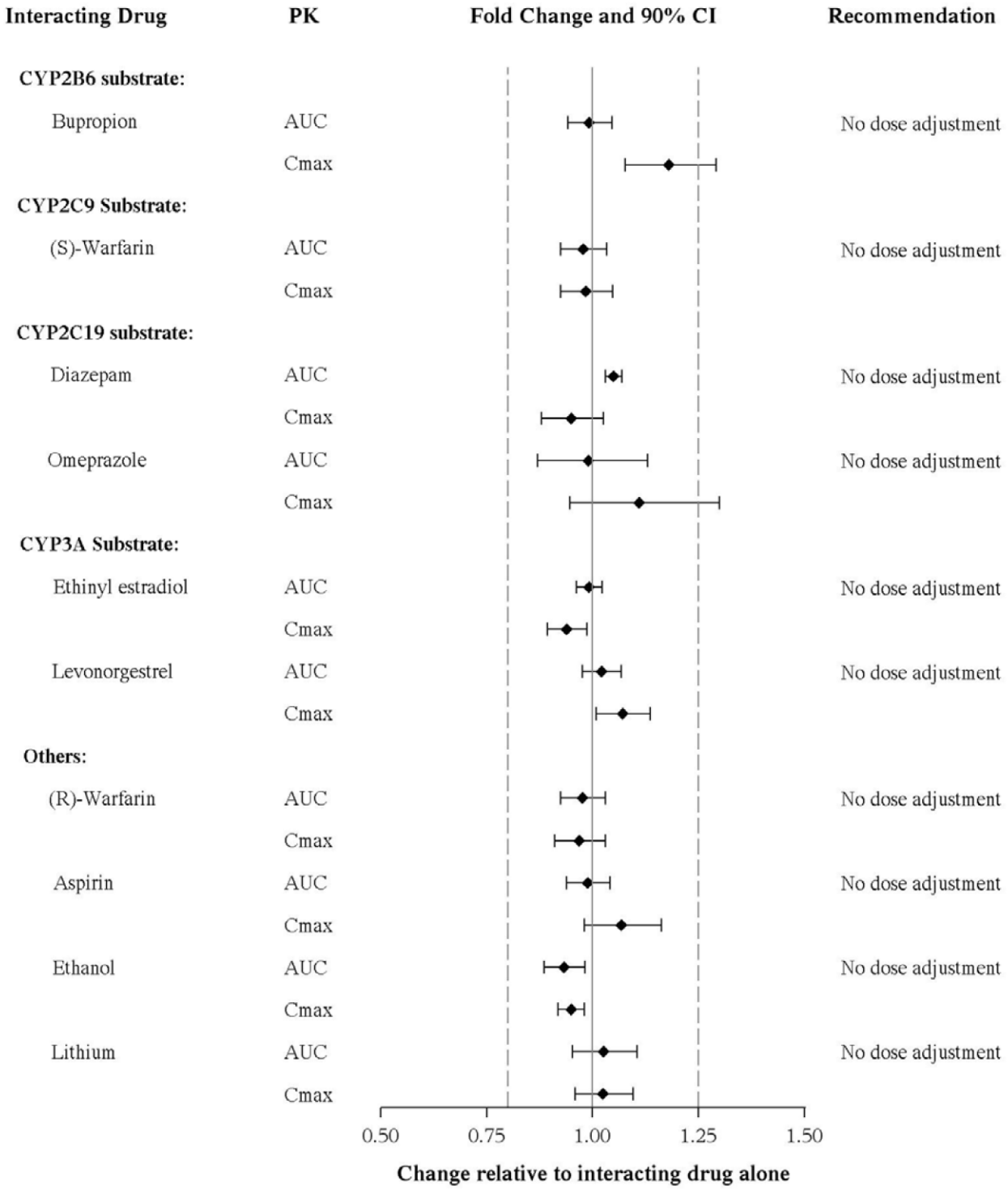
Vortioxetine and its metabolite(s) are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, P-gp, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. As such, no clinically relevant interactions with drugs metabolized/transported by these CYP enzymes or transporters would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of TRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of TRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2)*.

Because vortioxetine is highly bound to plasma protein, coadministration of TRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug.

However, in a clinical study with coadministration of TRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions (7.2)]*.

Figure 2. Impact of Vortioxetine on PK of Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited human data on TRINTELLIX use during pregnancy to inform any drug-associated risks. However, there are clinical considerations regarding neonates exposed to SSRIs and SNRIs, including TRINTELLIX, during the third trimester of pregnancy *[see Clinical Considerations]*. Vortioxetine administered to pregnant rats and rabbits during the period of organogenesis at doses ≥15 times and 10 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight and delayed ossification. No malformations were seen at doses up to 77 times and 58 times the MRHD, respectively. Vortioxetine administered to pregnant rats during gestation and lactation at oral doses ≥20 times the MRHD resulted in a decrease in the number of live-born pups and an increase in early postnatal pup mortality. Decreased pup weight at birth to weaning occurred at 58 times the MRHD and delayed physical development occurred at ≥20 times the MRHD. These effects were not seen at 5 times the MRHD *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal adverse reactions

Exposure to serotonergic antidepressants, including TRINTELLIX, in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). Monitor neonates who were exposed to TRINTELLIX in the third trimester of pregnancy for PPHN and drug discontinuation syndrome *[see Data]*.

Data

Human Data

Third Trimester Exposure

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. These findings are based on postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly, a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the

general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 - 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Animal Data

In pregnant rats and rabbits, no malformations were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, in rats and rabbits, respectively. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses of 40 and 120 mg/kg (20 and 58 times the MRHD, respectively) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

8.2 Lactation

Risk Summary

There is no information regarding the presence of vortioxetine in human milk, the effects on the breastfed infant, or the effects on milk production. Vortioxetine is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRINTELLIX and any potential adverse effects on the breastfed child from TRINTELLIX or from the underlying maternal condition.

Data

Animal Data

Administration of [^{14}C]-vortioxetine to lactating rats at an oral dose of 20 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, resulted in drug-related material in milk secretion. Milk to plasma ratio in lactating rats was 1, 1.2, 0.5, and 0.5 at 2, 6, 24, and 72 hours post dose.

8.4 Pediatric Use

Clinical studies on the use of TRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRINTELLIX in the pediatric population have not been established.

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these

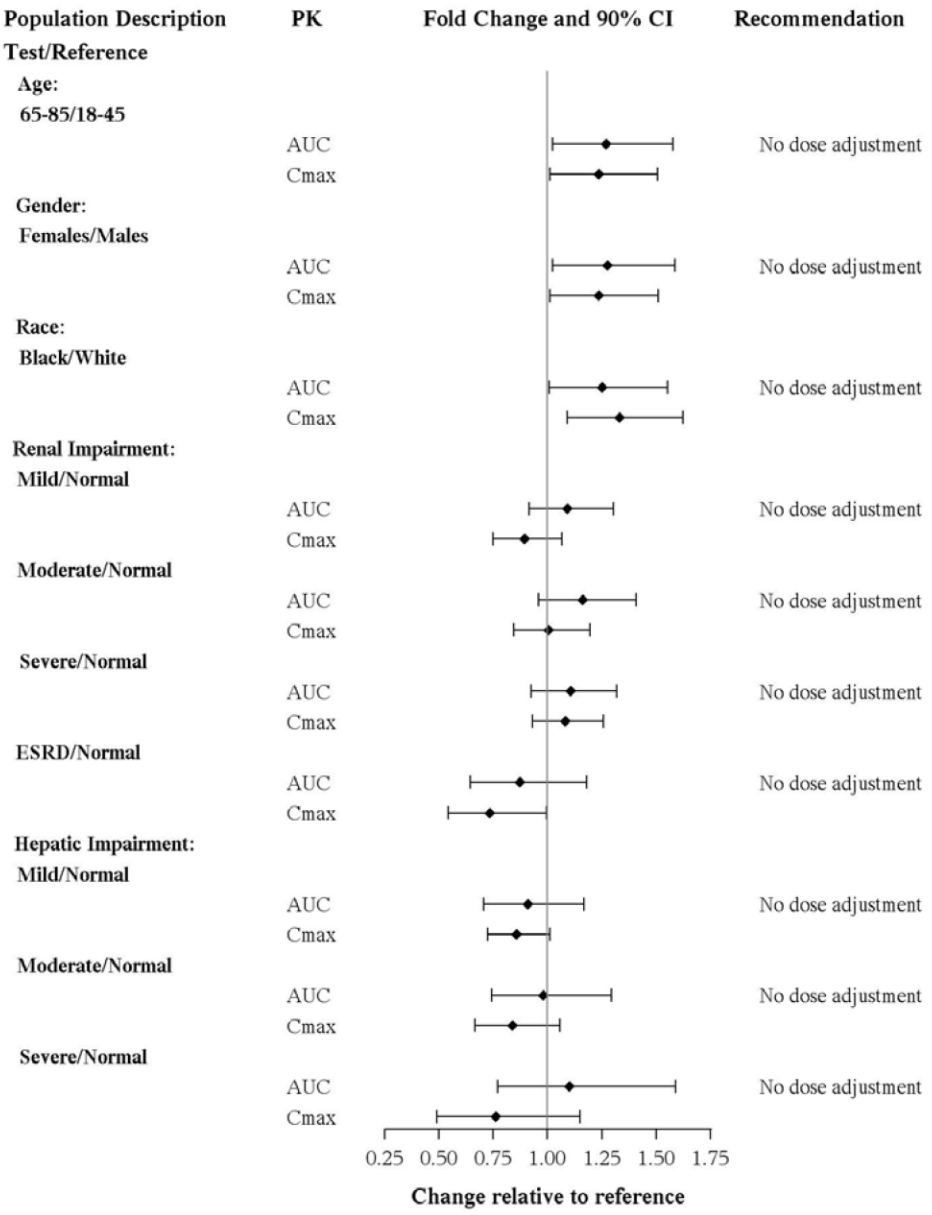
subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.6)]*.

8.6 Use in Other Patient Populations

No dose adjustment of TRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to severe hepatic impairment *(Figure 3) [see Clinical Pharmacology (12.3)]*.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



9 DRUG ABUSE AND DEPENDENCE

TRINTELLIX is not a controlled substance.

10 OVERDOSAGE

10.1 Human Experience

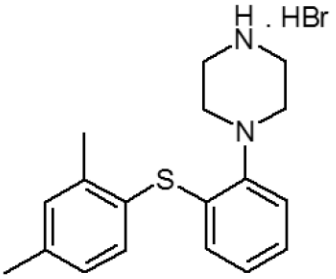
There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In premarketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of TRINTELLIX in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

10.2 Management of Overdose

No specific antidotes for TRINTELLIX are known. In managing overdosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

TRINTELLIX is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr), an antidepressant. Vortioxetine HBr is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. The empirical formula is $C_{18}H_{22}N_2S$, HBr with a molecular weight of 379.36 g/mol. The structural formula is:



Vortioxetine HBr is a white to very slightly beige powder that is slightly soluble in water.

Each TRINTELLIX tablet contains 6.355 mg, 12.71 mg or 25.42 mg of vortioxetine HBr equivalent to 5 mg, 10 mg, or 20 mg of vortioxetine, respectively. The inactive ingredients in TRINTELLIX tablets include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating which consists of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg and 20 mg) and iron oxide yellow (10 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

12.2 Pharmacodynamics

Vortioxetine binds with high affinity to the human serotonin transporter (Ki=1.6 nM), but not to the norepinephrine (Ki=113 nM) or dopamine (Ki>1000 nM) transporters. Vortioxetine potently

and selectively inhibits reuptake of serotonin (IC50=5.4 nM). Vortioxetine binds to 5-HT3 (Ki=3.7 nM), 5-HT1A (Ki=15 nM), 5-HT7 (Ki=19 nM), 5-HT1D (Ki=54 nM), and 5-HT1B (Ki=33 nM), receptors and is a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

In humans, the mean 5-HT transporter occupancy, based on the results from two clinical PET studies using 5-HTT ligands ([^{11}C]-MADAM or [^{11}C]-DASB), was approximately 50% at 5 mg/day, 65% at 10 mg/day and approximately 80% at 20 mg/day in the regions of interest.

Effect on Cardiac Repolarization
The effect of vortioxetine 10 mg and 40 mg administered once daily on QTc interval was evaluated in a randomized, double-blind, placebo-, and active-controlled (moxifloxacin 400 mg), four-treatment-arm parallel study in 340 male subjects. In the study the upper bound of the one-sided 95% confidence interval for the QTc was below 10 ms, the threshold for regulatory concern. The oral dose of 40 mg is sufficient to assess the effect of metabolic inhibition.

Effect on Driving Performance
In a clinical study in healthy subjects, TRINTELLIX did not impair driving performance, or have adverse psychomotor or cognitive effects following single and multiple doses of 10 mg/day.

12.3 Pharmacokinetics
Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steady-state plasma concentrations are typically achieved within two weeks of dosing.

Absorption
The maximal plasma vortioxetine concentration (C_{max}) after dosing is reached within 7 to 11 hours postdose (T_{max}). Steady-state mean C_{max} values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution
The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate or severe) or renal (mild, moderate, severe, ESRD) impairment is observed.

Metabolism and Elimination
Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers.

Following a single oral dose of [^{14}C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild, moderate or severe) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which CD-1 mice and Wistar rats were given oral doses of vortioxetine up to 50 and 100 mg/kg/day for male and female mice, respectively, and 40 and 80 mg/kg/day for male and female rats, respectively, for two years. The doses in the two species were approximately 12, 24, 20, and 39 times, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

In rats, the incidence of benign polypoid adenomas of the rectum was statistically significantly increased in females at doses 39 times the MRHD, but not at 15 times the MRHD. These were considered related to inflammation and hyperplasia and possibly caused by an interaction with a vehicle component of the formulation used for the study. The finding did not occur in male rats at 20 times the MRHD.

In mice, vortioxetine was not carcinogenic in males or females at doses up to 12 and 24 times, respectively, the MRHD.

Mutagenicity

Vortioxetine was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay in cultured human lymphocytes, and an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Treatment of rats with vortioxetine at doses up to 120 mg/kg/day had no effect on male or female fertility, which is 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of TRINTELLIX in treatment for MDD was established in six, 6 to 8 week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

Adults (aged 18 years to 75 years)

The efficacy of TRINTELLIX in patients aged 18 years to 75 years was demonstrated in five, 6 to 8 week, placebo-controlled studies (Studies 1 to 5 in *Table 4*). In these studies, patients were randomized to TRINTELLIX 5 mg, 10 mg, 15 mg or 20 mg or placebo once daily. For patients who were randomized to TRINTELLIX 15 mg/day or 20 mg/day, the final doses were titrated up from 10 mg/day after the first week.

The primary efficacy measures were the Hamilton Depression Scale (HAMD-24) total score in Study 2 and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in all other studies. In each of these studies, at least one dose group of TRINTELLIX was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement *(see Table 4)*. Subgroup analysis by age, gender or race did not suggest any clear evidence of differential responsiveness. Two studies of the 5 mg dose in the U.S. (not represented in *Table 4*) failed to show effectiveness.

Elderly Study (aged 64 years to 88 years)

The efficacy of TRINTELLIX for the treatment of MDD was also demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study of TRINTELLIX in elderly patients (aged 64 years to 88 years) with MDD (Study 6 in *Table 4*). Patients meeting the diagnostic criteria for recurrent MDD with at least one previous major depressive episode before the age of 60 years

and without comorbid cognitive impairment (Mini Mental State Examination score <24) received TRINTELLIX 5 mg or placebo.

Table 4. Primary Efficacy Results of 6 Week to 8 Week Clinical Trials

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
Study 1 [MADRS] Non-US Study	TRINTELLIX (5 mg/day)‡	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	TRINTELLIX (10 mg/day)‡	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	TRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	TRINTELLIX (10 mg/day)‡	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	TRINTELLIX (15 mg/day) ‡	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	TRINTELLIX (20 mg/day) ‡	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	TRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	TRINTELLIX (20 mg/day) ‡	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	TRINTELLIX (10 mg/day)	154	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	TRINTELLIX (20 mg/day) ‡	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	TRINTELLIX (5 mg/day) ‡	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

† Difference (drug minus placebo) in least-squares mean change from baseline.

‡ Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse).

Time Course of Treatment Response

In the 6 to 8 week placebo-controlled studies, an effect of TRINTELLIX based on the primary efficacy measure was generally observed starting at Week 2 and increased in subsequent weeks with the full antidepressant effect of TRINTELLIX generally not seen until Study Week 4 or later. *Figure 4* depicts time course of response in U.S. based on the primary efficacy measure (MADRS) in Study 5.

Figure 4. Change from Baseline in MADRS Total Score by Study Visit (Week) in Study 5

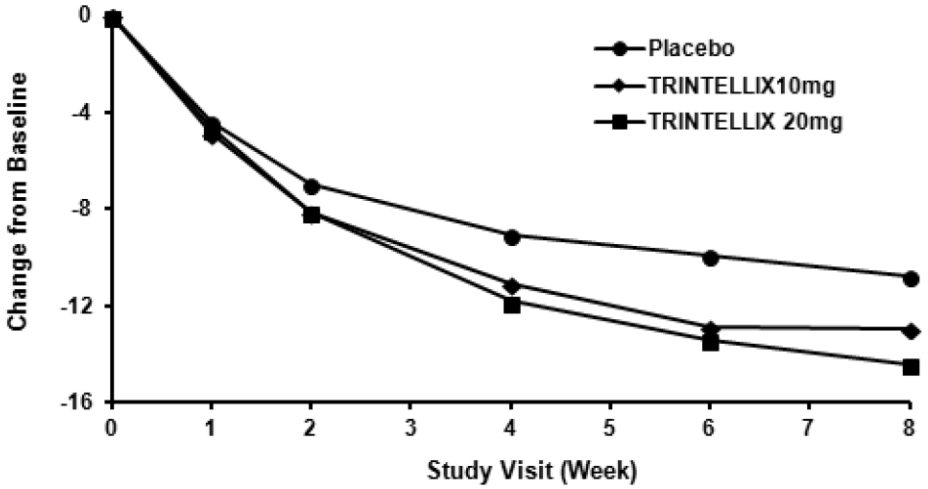
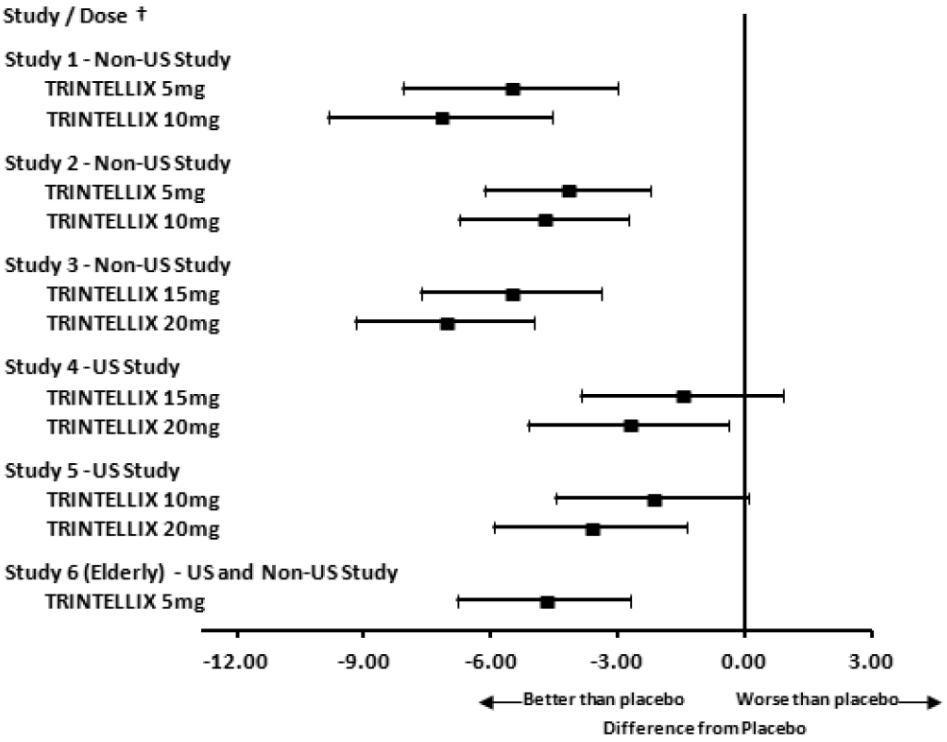


Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8



† Results (point estimate and unadjusted 95% confidence interval) are from mixed model for repeated measures (MMRM) analysis. In Studies 1 and 6, the primary analysis was not based on MMRM and in Studies 2 and 6 the primary efficacy measure was not based on MADRS.

Digit Symbol Substitution Test in Major Depressive Disorder

Two, eight week, randomized, double-blind, placebo-controlled studies were conducted to evaluate the effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST) during the treatment of acute MDD. The DSST is a neuropsychological test that most specifically measures processing speed, an aspect of cognitive function that may be impaired in MDD. Patients are asked to match nine symbols with their corresponding number (1 to 9) according to a key; the score is the correct number of matches achieved in 90 seconds. For reference, the mean score for healthy 45 to 54 year-old subjects is 50 (SD=15).

Study 7 randomized adult patients meeting the diagnostic criteria for recurrent MDD to receive TRINTELLIX 10 mg, TRINTELLIX 20 mg, or placebo once daily. Study 8 randomized adult patients meeting the diagnostic criteria for recurrent MDD and reporting subjective difficulty concentrating or slow thinking to receive a flexible dose of TRINTELLIX (10 or 20 mg) or placebo once daily. Neither study included patients whose MDD was in remission yet who continued to experience difficulty concentrating or slow thinking. Patients' mean age was 46 (SD=12) and 45 (SD=12) in Study 7 and 8, respectively. In both studies, patients in the TRINTELLIX group had a statistically significantly greater improvement in number of correct responses on the DSST *(Table 5)*; depressed mood as assessed by change from baseline in MADRS total score also improved in both studies.

Table 5. Effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST)

Study No.	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference§ (95% CI)
Study 7	TRINTELLIX (10 mg/day)‡	193	42.0 (12.6)	9.0 (0.6)	4.2 (2.5, 5.9)
	TRINTELLIX (20 mg/day)‡	204	41.6 (12.7)	9.1 (0.6)	4.3 (2.6, 5.9)
	Placebo	194	42.4 (13.8)	4.8 (0.6)	--
Study 8	TRINTELLIX (10/20 mg/day)‡	175	42.1 (11.9)	4.6 (0.5)	1.8 (0.3, 3.2)
	Placebo	167	43.0 (12.3)	2.9 (0.5)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

§ Difference (drug minus placebo) in least-squares mean change from baseline.

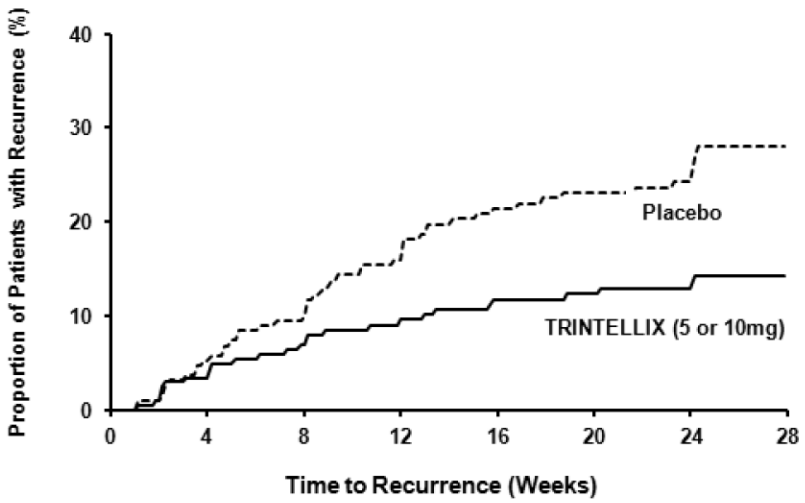
‡ Doses are statistically significantly superior to placebo.

The effects observed on DSST may reflect improvement in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage over other antidepressants on the DSST.

Maintenance Study

In a non-US maintenance study (Study 9 in *Figure 6*), 639 patients meeting DSM-IV-TR criteria for MDD received flexible doses of TRINTELLIX (5 mg or 10 mg) once daily during an initial 12 week open-label treatment phase; the dose of TRINTELLIX was fixed during Weeks 8 to 12. Three hundred ninety six (396) patients who were in remission (MADRS total score ≤10 at both Weeks 10 and 12) after open-label treatment were randomly assigned to continuation of a fixed dose of TRINTELLIX at the final dose they responded to (about 75% of patients were on 10 mg/day) during the open-label phase or to placebo for 24 to 64 weeks. Approximately 61% of randomized patients satisfied remission criterion (MADRS total score ≤10) for at least four weeks (since Week 8), and 15% for at least eight weeks (since Week 4). Patients on TRINTELLIX experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo. Recurrence of depressive episode was defined as a MADRS total score ≥22 or lack of efficacy as judged by the investigator.

Figure 6. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 9)



Prospective Evaluation of Treatment Emergent Sexual Dysfunction (TESD)

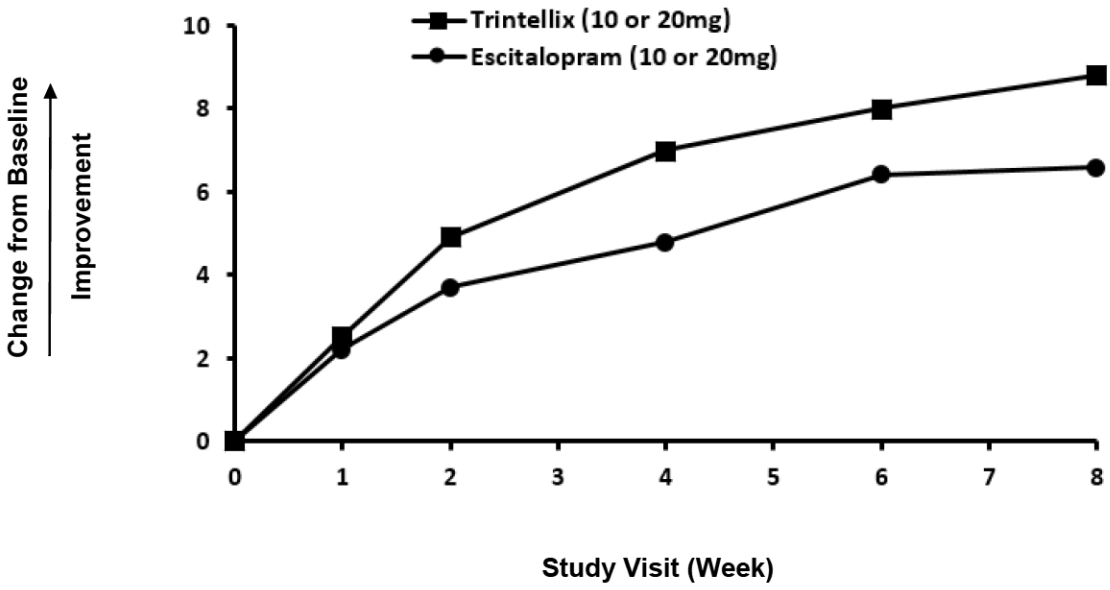
Two, randomized, double-blind, active-controlled studies were conducted to prospectively compare the incidence of TESD between TRINTELLIX and SSRIs via a validated self-rated measure of sexual function, the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). The CSFQ-14 is designed to measure illness- and medication-related changes in sexual functioning that consists of 14 items measuring sexual functioning as a total score. The CSFQ-14 consists of subscales that assess the three phases of the sexual response cycle (desire, arousal, and orgasm). Higher scores on the CSFQ-14 indicate greater sexual function and for reference, a 2-3 point change is considered clinically meaningful.

Effect of Switching from SSRI to TRINTELLIX on TESD

The effect of TRINTELLIX on TESD induced by prior SSRI treatment in MDD patients whose depressive symptoms were adequately treated was evaluated in an eight-week, randomized, double-blind, active-controlled (escitalopram), flexible-dose study (Study 10). Patients taking citalopram, sertraline, or paroxetine for at least eight weeks duration and who were experiencing sexual dysfunction attributed to their SSRI treatment were switched to TRINTELLIX (n=217) or escitalopram (n=207). For both TRINTELLIX and escitalopram, patients were started on 10 mg, increased to 20 mg at Week 1, followed by flexible dosing. The majority of subjects received the 20 mg dose of TRINTELLIX (65.6%) or the 20 mg dose of escitalopram (71.9%) during the study.

Improvement in TESD induced by prior SSRI treatment in subjects switched to TRINTELLIX was superior to the improvement observed in those subjects who switched to escitalopram (2.2 point improvement vs escitalopram on the change from Baseline in CSFQ-14 total score, with 95% confidence interval 0.48 – 4.02), after eight weeks of treatment, while both drugs maintained the subjects' prior antidepressant response. For change from Baseline in CSFQ-14, *see Figure 7*.

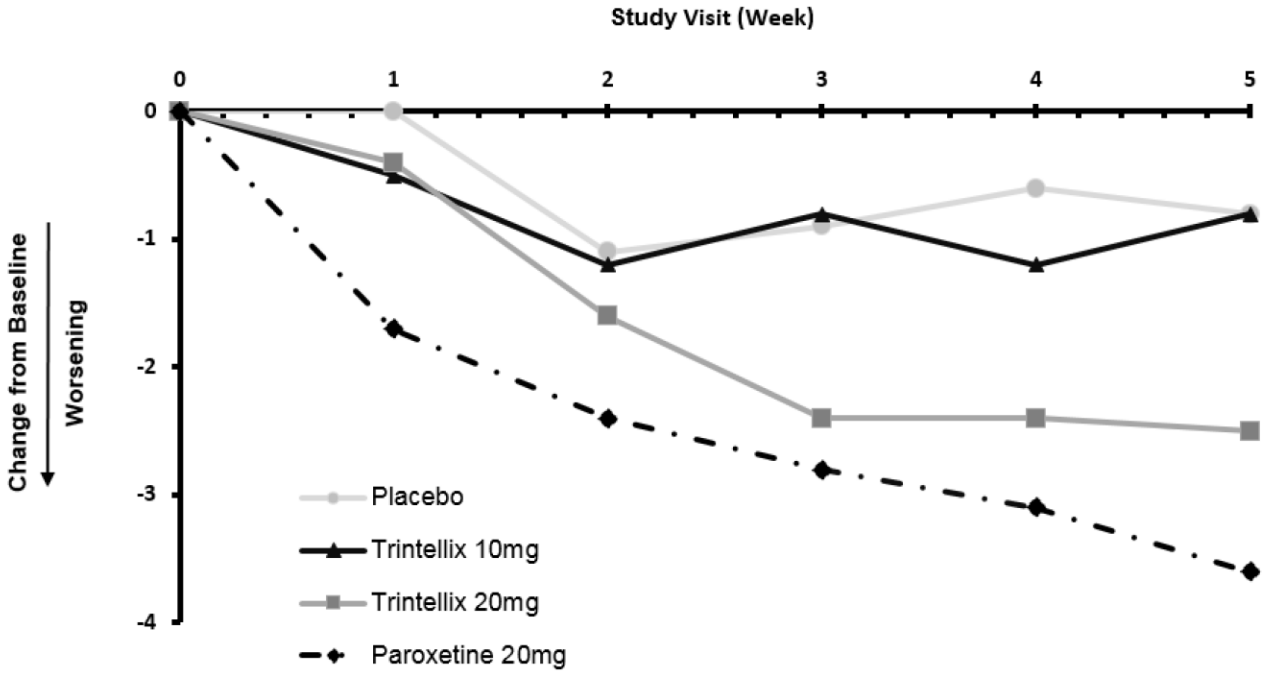
Figure 7. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Study 10



Effects in Healthy Volunteers with Normal Sexual Functioning at Baseline

In a randomized Healthy Volunteer study (Study 11) with 348 subjects aged 18 years to 40 years with normal sexual functioning without the confounding effect of depression, TESD with TRINTELLIX 10 mg (n=85), but not with TRINTELLIX 20 mg (n=91), was statistically significantly less than with paroxetine 20 mg (n=83) *[see Adverse Reactions (6.1)]*. Paroxetine 20 mg was statistically significantly worse than placebo (n=89), confirming assay sensitivity in this study. For change from Baseline in CSFQ-14, *see Figure 8*.

Figure 8. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Healthy Volunteers (Study 11)



16 HOW SUPPLIED/STORAGE AND HANDLING

TRINTELLIX tablets are available as follows:

Features	Strengths		
	5 mg	**10 mg**	**20 mg**
Color	pink	yellow	red
Debossment	"5" on one side of tablet "TL" on other side of tablet	"10" on one side of tablet "TL" on other side of tablet	"20" on one side of tablet "TL" on other side of tablet
Presentations and NDC Codes			
Bottles of 30	64764-720-30	64764-730-30	64764-750-30
Bottles of 90	64764-720-90	64764-730-90	64764-750-90
Bottles of 500	64764-720-77	64764-730-77	64764-750-77

Storage: Store at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients and their caregivers about the benefits and risks associated with treatment with TRINTELLIX and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially early during treatment and when the dose is adjusted up or down *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Discontinuation of Treatment
Patients who are on TRINTELLIX 15 mg/day or 20 mg/day may experience headache, muscle tension, mood swings, sudden outburst of anger, dizziness and runny nose if they abruptly stop their medicine. Advise patients not stopping TRINTELLIX without talking to their healthcare provider *[see Adverse Reactions (6)]*.

Concomitant Medication
Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications because of a potential for interactions. Instruct patients not to take TRINTELLIX with an MAOI or within 14 days of stopping an MAOI and to allow 21 days after stopping TRINTELLIX before starting an MAOI *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7.1)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of TRINTELLIX and triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan supplements, and St. John's Wort supplements *[see Warnings and Precautions (5.2), Drug Interactions (7.1, 7.2)]*.

Abnormal Bleeding
Caution patients about the increased risk of abnormal bleeding when TRINTELLIX is given with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation *[see Warnings and Precautions (5.3)]*.

Activation of Mania/Hypomania
Advise patients and their caregivers to look for signs of activation of mania/hypomania *[see Warnings and Precautions (5.4)]*.

Angle Closure Glaucoma
Patients should be advised that taking TRINTELLIX can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.5)]*.

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking TRINTELLIX *[see Warnings and Precautions (5.6)]*.

Nausea
Advise patients that nausea is the most common adverse reaction, and is dose related. Nausea commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients.

Alcohol
A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg/day) did not increase the impairment of mental and motor skills caused by alcohol.

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise a pregnant woman or a woman planning to become pregnant that TRINTELLIX may cause withdrawal symptoms in the newborn or persistent pulmonary hypertension of the newborn (PPHN) *[see Use in Specific Populations (8.1)]*.

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