種類	受付番号	実施日	記録番号
）			
医薬品相談（ ）		平成 （20 ）年 月 日	号
医薬品相談（ ）		平成 （20 ）年 月 日	号
医薬品相談（ ）		平成 （20 ）年 月 日	号
医薬品相談（ ）		平成 （20 ）年 月 日	号
医薬品相談（ ）		平成 （20 ）年 月 日	号
医薬品相談		平成 （20 ）年 月 日	号
医薬品相談		平成 （20 ）年 月 日	－
医薬品相談（書面）		平成 （20 ）年 月 日	号
医薬品相談		平成 （20 ）年 月 日	号
医薬品相談		平成 （20 ）年 月 日	号
医薬品相談（ ）		（20 ）年 月 日	号
医薬品相談（ ）		（20 ）年 月 日	号

3.4.1 相談（ ）【1.13.2.01】

について

について

は結果を踏まえ、次の理由からでの し、統合失調症を対象とした（ ）を することを提案した。

(1) していることから、できる

(2) していることからできる

その結果、、及び ため、及び ことを目的とした に し、その際には の できるように する助言を得た。また、は、は統合失調症という疾患及び の を考慮し（ の ）の での実施の助言を得た。これらの助言を踏まえて、及び

[redacted]、更に、[redacted]する目的で統合失調症を対象とした[redacted]を実施することとした。

3.4.2　医薬品[redacted]相談（[redacted]）【1.13.2.02】

[redacted]について

[redacted]（[redacted]）の結果を踏まえ、[redacted]を相談した。[redacted]及び[redacted]相談の助言から、[redacted]を[redacted]、[redacted]を[redacted]としたランダム化二重盲検第 3 相試験を計画することとした。また、統合失調症を対象とした[redacted]、[redacted]や[redacted]を考慮すると、[redacted]、[redacted]として実施することとした。

[redacted]、[redacted]は、[redacted]で[redacted]が得られなかったことから、[redacted]として[redacted]と[redacted]の[redacted]し、[redacted]及び[redacted]ことが適切であるとの助言を得た。また、[redacted]での[redacted]で[redacted]と[redacted]、[redacted]の[redacted]は[redacted]、[redacted]を可能な限り[redacted]との助言を得た。これらを踏まえ、[redacted]、[redacted]、[redacted]及び[redacted]とし、[redacted]は「国際共同治験に関する基本的考え方について（平成 19 年 9 月 28 日、薬食審査発第 0928010 号）」に基づき[redacted]し[redacted]することとした。[redacted]や[redacted]は、改めて[redacted]とした（3.4.3 項参照）。

[redacted]について

[redacted]に関連し、[redacted]を[redacted]（[redacted]とすることなど）を[redacted]、[redacted]ための[redacted]及び[redacted]を[redacted]ことから、実施中の[redacted]（[redacted]）の[redacted]との助言を得た。これを踏まえ、[redacted]の[redacted]など[redacted]を変更し、[redacted]した。

3.4.3　医薬品[redacted]相談（[redacted]）【1.13.2.03】

[redacted]について

医薬品[redacted]相談（[redacted]）及び[redacted]（[redacted]、[redacted]、[redacted]）での[redacted]の結果を踏まえ、[redacted]を提案した。機構の助言を踏まえて[redacted]、[redacted]、かつ[redacted]と[redacted]ことで、[redacted]を[redacted]ことは可能であるとの助言を得た。

3.4.4　医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談[redacted]（[redacted]）【1.13.2.04, 1.13.2.05】

[redacted]（[redacted]、[redacted]）[redacted]及び[redacted]について（[redacted]）

医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談（[redacted]）[redacted]、日本、台湾及び韓国で Pan-Asia P3 試験（P3-J002 試験）を実施したが、主要評価項目である投与終了時の PANSS 合計スコアでルラシドンのプラセボに対する優越性が検証できなかったことから、[redacted]し、[redacted]した。[redacted]（[redacted]及び[redacted]）を踏まえ、[redacted]、[redacted]とした。

3.4.5　医薬品[redacted]相談（[redacted]）【1.13.2.06】

[redacted]及び[redacted]

米国を中心に実施した双極 I 型障害の大うつ病エピソードの患者を対象とした第 3 相プラセボ対照試験でルラシドンの有効性が検証され、米国及びカナダに承認申請が行われたことから、本邦でも双極性障害のうつ症状及び[redacted]することとした。[redacted]で双極 I 型障害の大うつ病エピソードの患者を対象とした[redacted]及び[redacted]する目的で[redacted]を提案した。なお、[redacted]の[redacted]は、[redacted]に対する[redacted]こと、[redacted]ことを前提として、[redacted]と[redacted]と[redacted]を提案した。

対面助言での機構の助言を踏まえ、[redacted]（[redacted]）、[redacted]（[redacted]）を[redacted]こととした。また、[redacted]（[redacted]）に[redacted]を[redacted]とした。なお、[redacted]は[redacted]に基づき結論されるべきとの助言を得た。

3.4.6　医薬品[redacted]相談（[redacted]）【1.13.2.07, 1.13.2.08, 1.13.2.09, 1.13.2.10, 1.13.2.11, 1.13.2.12】

平成[redacted]（20[redacted]）年[redacted]月[redacted]日に[redacted]に関して、医薬品[redacted]相談（[redacted]：[redacted]）[redacted]、平成[redacted]（20[redacted]）年[redacted]月[redacted]日付及び同年[redacted]月[redacted]日付の[redacted]

[redacted]した。機構の意見及び助言を踏まえ、医薬品承認販売申請を行うこととした。なお、[redacted]、[redacted]及び[redacted]については、[redacted]した。

3.4.7　医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談（[redacted]）

(1)　医薬品[redacted]相談（[redacted]）【1.13.2.13】

[redacted]について

[redacted]について

医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談（[redacted]）[redacted]、日本、台湾、マレーシア及び韓国で Pan-Asia 追加 P3 試験（P3-J056 試験）を実施したが、主要評価項目である投与終了時のベースラインからの PANSS 合計スコア変化量でルラシドンのプラセボに対する優越性が検証できなかったことから、[redacted]し、[redacted]提案した。機構から得られた助言の概要は以下の通り。

- [redacted]ために、[redacted]、[redacted]だが、[redacted]ことに[redacted]場合、[redacted]、[redacted]及び[redacted]を[redacted]について[redacted]が[redacted]を考慮すると、[redacted]について議論した上で[redacted]（[redacted]）[redacted]に[redacted]ことも一案であると考える。
- ただし、[redacted]（[redacted]）の[redacted]場合、[redacted]。統合失調症の薬物治療の現状を踏まえると、治療で効果が十分に得られない場合、すぐに他剤に変更することは困難であること、また安易に多剤併用療法が選択されることは好ましくないことから、[redacted]場合に[redacted]は[redacted]と考える。
- [redacted]を[redacted]、[redacted]で[redacted]を[redacted]ことが可能となるのか、検討する必要がある。

機構からの助言を踏まえ、[redacted]として設定した試験の[redacted]並びに[redacted]場合の[redacted]及び[redacted]について検討した上で、[redacted]については[redacted]とした。

[redacted]に[redacted]をする場合の[redacted]について

[redacted]のための[redacted]に[redacted]をする場合の[redacted]を提案したところ、機構からは、[redacted]などから[redacted]を[redacted]ことは[redacted]、[redacted]には、[redacted]と[redacted]

[redacted]と考えるとの助言を得た。

(2) 医薬品[redacted]相談（[redacted]）【1.13.2.14】

[redacted]

[redacted]に関する相談

[redacted]を、[redacted]、[redacted]及び[redacted]の[redacted]とする場合の[redacted]ことから、[redacted]及び[redacted]の[redacted]すること、また、[redacted]を[redacted]とする際の考え方について提案した。機構から得られた助言の概要は以下の通り。

- [redacted]を[redacted]とする場合の[redacted]について、[redacted]ため、[redacted]については、[redacted]（[redacted]及び[redacted]）で[redacted]と考える。
- 現時点では、[redacted]の結果、[redacted]の[redacted]が[redacted]、かつ[redacted]の[redacted]ことを前提に、[redacted]を[redacted]ためには、[redacted]の結果を踏まえ、[redacted]、及び[redacted]を説明する必要があると考えるため、承認申請時までに十分に検討すること。

相談結果を踏まえ、[redacted]及び[redacted]し、更に[redacted]とした。

3.4.8 医薬品[redacted]相談[redacted]（[redacted]）【1.13.2.15】

[redacted]

双極性障害うつの適応のためのピボタル試験である BP-P3-J001 試験でルラシドンの有効性が検証された。一方で、[redacted]BP-P3-J296 試験では有効性が検証されなかったことから、[redacted]。[redacted]の[redacted]及び[redacted]では、[redacted]に加え、[redacted]が[redacted]の[redacted]、[redacted]として[redacted]する予定としていた。したがって、[redacted]にあたっては、[redacted]、[redacted]、[redacted]、[redacted]を含めた[redacted]で、[redacted]ことを提案した。機構からは、[redacted]及び[redacted]の結果から、[redacted]により[redacted]に[redacted]いることを踏まえると、今後[redacted]ことを前提とすれば、[redacted]との助言を得た。また、[redacted]

[redacted]についても、[redacted]必要があるとの助言を得た。

3.4.9　医薬品[redacted]相談（[redacted]）【1.13.2.16】

[redacted]

医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談（[redacted]）[redacted]で、[redacted]の[redacted]ことを前提に、統合失調症、双極性障害うつ及び[redacted]を説明し、[redacted]した。機構から得られた助言の概要は以下の通り。

- [redacted]において[redacted]、[redacted]では[redacted]より[redacted]で[redacted]。また、BP-P3-J001 試験では、[redacted]、ルラシドン 20～60 mg/日群の有効性は検証されたものの、高用量群である 80～120 mg/日群の有効性は検証されていない。よって、[redacted]で、[redacted]が[redacted]、[redacted]から、[redacted]において[redacted]することは[redacted]ことから、[redacted]に基づき、[redacted]として[redacted]と考える。ただし、[redacted]については、[redacted]において、[redacted]及び[redacted]をはじめ、[redacted]した上で、[redacted]も踏まえて判断したいと考える。
- BP-P3-J001 試験でルラシドン 80～120 mg/日の有効性が示されなかった一因として、[redacted]。[redacted]が[redacted]、[redacted]においても[redacted]より[redacted]が認められていることから、[redacted]の[redacted]、[redacted]において、[redacted]と考える。ただし、[redacted]については、[redacted]において、[redacted]した上で、[redacted]も踏まえて判断したいと考える。
- [redacted]において、[redacted]の[redacted]は[redacted]ことから「[redacted]」を[redacted]とした[redacted]と考える。

[redacted]及び[redacted]

[redacted]に関する[redacted]ことで、[redacted]及び[redacted]の[redacted]、また、[redacted]に関する[redacted]した場合の[redacted]に関して機構の見解を確認した。その結果、[redacted]は[redacted]における[redacted]及び[redacted]ことを可能とし、結果として[redacted]こと、[redacted]との見解を得た。

3.4.10 医薬品[redacted]相談（[redacted]）【1.13.2.17】

[redacted]

医薬品[redacted]相談（[redacted]）及び医薬品[redacted]相談（[redacted]）[redacted]P3-J066 試験で、ルラシドン 40 mg/日の有効性が検証されたことから、[redacted]し、[redacted]における[redacted]を[redacted]とすることの[redacted]及び[redacted]と[redacted]を説明した。機構から得られた助言の概要は以下の通り。

- 「[redacted]での[redacted]及び[redacted]である」と[redacted]と考えるが、[redacted]に対する[redacted]に[redacted]することは可能と考える。なお、[redacted]における[redacted]であることから、[redacted]を[redacted]ことの適切性については、[redacted]において、[redacted]も踏まえて最終的に判断したいと考える。
  - [redacted]における解析は、[redacted]について[redacted]であり、その[redacted]については[redacted]こと等も踏まえると、[redacted]については、[redacted]において慎重に判断する必要があると考える。
  - [redacted]、[redacted]における[redacted]については主に[redacted]の結果をもとに評価すべきであり、[redacted]において[redacted]になると考える。

[redacted]及び[redacted]

[redacted]及び[redacted]について相談したところ、以下の助言を得た。

- [redacted]における[redacted]及び[redacted]の[redacted]は[redacted]及び[redacted]で、[redacted]における[redacted]は[redacted]であると考えることから、これらの[redacted]の[redacted]と考えている。
- しかしながら、[redacted]において、[redacted]及び[redacted]についても検討した上で、[redacted]の適切性を最終的に判断したい。

3.4.11 医薬品[redacted]相談（[redacted]）【1.13.2.18, 1.13.2.19】

平成[redacted]（20[redacted]）年[redacted]月[redacted]日に[redacted]（[redacted]）に関して、医薬品[redacted]相談（[redacted]：[redacted]）を[redacted]、[redacted]（20[redacted]）年[redacted]月[redacted]日付及び同年[redacted]月[redacted]日付の[redacted]した。機構の意見及び助言を踏まえ、医薬品承認販売申請を行うこととした。なお、[redacted]、[redacted]及び[redacted]については、[redacted]した。

3.5　承認申請に用いる臨床パッケージ

ルラシドン統合失調症の適応としては、平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）、平成[redacted]（20[redacted]）年[redacted]月[redacted]日までに[redacted]（[redacted]）、平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）とその[redacted]［平成[redacted]（20[redacted]）年[redacted]月[redacted]日、[redacted]）及び平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）を踏まえて、海外の統合失調症を対象とした試験及び臨床薬理試験データを可能な限り利用する臨床試験データパッケージを構成した。臨床試験パッケージのうち、すべての国内臨床試験と海外 10 試験（プラセボ対照試験第 2 相 2 試験、第 3 相 4 試験、長期 3 試験及び臨床薬理 1 試験）を評価資料とし、その他の試験は参考資料とした。

双極性障害うつの適応としては、平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）、平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）及び平成[redacted]（20[redacted]）年[redacted]月[redacted]日に実施した[redacted]（[redacted]）を踏まえて、国内の統合失調症を対象とした試験、国内外の双極性障害を対象とした試験及び臨床薬理試験データを可能な限り利用する臨床試験データパッケージを構成した。なお、第 1 相試験、臨床薬理試験に関しては統合失調症の臨床パッケージと兼ねている。

以上、本承認申請の臨床試験パッケージに基づき、以下の効能・効果、用法・用量にてルラシドンの医薬品製造販売承認申請を行うこととした。

効能・効果：
〇統合失調症
〇双極性障害におけるうつ症状の改善

用法・用量：
＜統合失調症＞
通常、成人にはルラシドン塩酸塩として 40 mg を 1 日 1 回食後経口投与する。
なお、年齢、症状により適宜増減するが、1 日量は 80 mg を超えないこと。
＜双極性障害におけるうつ症状の改善＞
通常、成人にはルラシドン塩酸塩として 20 mg を 1 日 1 回食後経口投与により開始する。
なお、年齢、症状により適宜増減するが、増量幅は 1 日量として 20 mg とし、1 日量は 60 mg を超えないこと。

なお、審査を踏まえて、＜双極性障害におけるうつ症状の改善＞の用法・用量を以下のとおり変更することとした。

通常、成人にはルラシドン塩酸塩として 20～60 mg を 1 日 1 回食後経口投与する。
なお、開始用量は 20 mg、増量幅は 1 日量として 20 mg とし、年齢、症状により適宜増減するが、1 日量は 60 mg を超えないこと。

4. 申請製剤及び申請効能以外の開発状況

申請製剤以外では[redacted]の[redacted]を[redacted]である。また、申請効能以外で[redacted]を[redacted]。

5. 外国での開発状況

米国では 2000 年 11 月に住友製薬アメリカ［現、サノビオン・ファーマシューティカルズ・インク（サノビオン社）］が米国食品医薬品局（FDA）に Investigational New Drug Application（IND）申請を行い、ルラシドンの開発を進めた。2005 年 6 月、MSD Pembroke LTD Ltd.（以下、Merck 社）にルラシドンの海外での開発権を導出し、Merck 社では[redacted]試験、[redacted]試験及び[redacted]試験などが行われた。その後、20[redacted]年には大日本住友製薬株式会社がその権利を再び獲得した。大日本住友製薬アメリカ（現、サノビオン社）が開発を再開し、Merck 社実施試験を含めて 2009 年 12 月に FDA に申請し、2010 年 10 月に成人の統合失調症（40～80 mg/日）を適応として承認された。2012 年 4 月には、120 mg/日及び 160 mg/日の用量拡大承認を取得し、米国での成人統合失調症患者に対する推奨用量は 40～160 mg/日となった。また、2011 年 3 月には、武田薬品工業株式会社と英国を除く EU 加盟国及びスイス、ノルウェー、トルコ、ロシアを対象国とした共同開発・独占的販売契約を締結した。2012 年 9 月に欧州医薬品庁（EMA）に申請し、2014 年 3 月に成人の統合失調症を適応として販売許可を取得した。なお、2015 年 5 月に武田薬品工業株式会社との欧州における共同開発・独占的販売契約の解消が決定し、現在は、Angelini S.p.A 社に、欧州 29 ヵ国及びトルコにおける独占的販売権を許諾し販売許可承認を移管してい

る。2019 年 3 月時点で、米国、カナダ、スイス、EU 加盟国、オーストラリア等の 45 の国及び地域で承認を取得している。青年期統合失調症患者の適応は、2017 年 1 月に米国で承認されて以来、2019 年 3 月現在では、米国、カナダ、オーストラリア及び台湾にて承認を取得している。

成人の双極性 I 型障害うつに対しては、単剤及び Li/VPA との併用療法の 2 つの適応で 2012 年 9 月に FDA に申請し、2013 年 6 月に承認を取得した。2019 年 3 月時点で、米国、カナダ、ブラジル、ロシア及び台湾で承認されている。小児の双極性 I 型障害うつの適応は、2018 年 3 月に米国で承認されて以来、2019 年 3 月現在では、米国及びカナダにて承認を取得している。

ルラシドン統合失調症及び双極性 I 型障害うつの各適応の米国での用法・用量を以下に示した。

＜米国で承認されている用法・用量＞

Indication	**Recommended Starting Dose**	**Recommended Dose**
Schizophrenia – adults	40 mg per day	40 mg to 160 mg per day
Schizophrenia – adolescents (13 to 17 years)	40 mg per day	40 mg to 80 mg per day
Depressive episode associated with Bipolar I Disorder (Bipolar Depression) – adults	20 mg per day	20 mg to 120 mg per day
Depressive episode associated with Bipolar I Disorder (Bipolar Depression) – pediatric patients (10 to 17 years)	20 mg per day	20 mg to 80 mg per day

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図 1.5- 2　開発の経緯図（製剤開発及び品質に関する試験）

資料区分	試験項目		[redacted]	添付資料番号
品質に関する試験	原薬	特性		3.2.S.1.3 3.2.S.3.1
		製造		3.2.S.2.5-6
		品質評価		3.2.S.4 3.2.S.5
		安定性		3.2.S.7.1 3.2.S.7.3
	製剤	製造		3.2.P.2
		品質評価		3.2.P.5
		安定性		3.2.P.8.1 3.2.P.8.3

図 1.5- 3　開発の経緯図（非臨床試験）

資料区分	試験項目		添付資料番号
薬理試験	効力を裏付ける試験		4.2.1.1.01-5, 4.2.1.1.08, 4.2.1.1.12-27, 36
	副次的薬理試験		4.2.1.2.01, 4.2.1.2.09-10
	安全性薬理試験		4.2.1.3.01, 4.2.1.3.03, 4.2.1.3.05-23
薬物動態試験	分析法		4.2.2.1.02-04
	吸収		4.2.2.2.02-05
	分布		4.2.2.2.03-05 4.2.2.3.01-03
	代謝		4.2.2.4.02-03, 4.2.2.4.05-08, 11, 5.3.2.2.01, 03, 04
	排泄		4.2.2.2.03-05 4.2.2.4.02 4.2.2.4.05-08 4.2.2.5.01
	薬物動態学的相互作用（非臨床）		5.3.2.2.07, 09-12
毒性試験	単回投与毒性試験		4.2.3.1.01-03
	反復投与毒性試験		4.2.3.2.01-10
	遺伝毒性試験		4.2.3.3.1.01-02, 4.2.3.3.2.01
	がん原性試験		4.2.3.4.1.01-02
	生殖発生毒性試験		4.2.3.5.1.01-02, 4.2.3.5.2.01-02, 4.2.3.5.2.05-06, 4.2.3.5.3.01, 4.2.3.5.4.01
	その他の毒性試験		4.2.3.7.1.01, 4.2.3.7.4.01, 4.2.3.7.5.01-02, 4.2.3.7.7.01-04

*評価資料のみを記載

図 1.5- 4　開発の経緯図（臨床試験）

*評価資料のみを記載

対象	試験項目		添付資料番号
健康成人、統合失調症患者	臨床薬理		5.3.1.2.01 5.3.3.1.03 5.3.3.2.01 5.3.3.3.01 5.3.4.2.01
健康成人	第 1 相		5.3.1.1.01 5.3.3.1.01 5.3.3.1.02 5.3.3.4.01
統合失調症患者	第 2 相（海外）		5.3.5.1.09-S 5.3.5.1.12-S
	第 2 相（国内）		5.3.5.1.03-S 5.3.5.2.01-S
	第 3 相（海外）		5.3.5.1.04-S 5.3.5.1.05-S 5.3.5.1.06-S 5.3.5.1-16-S
	第 3 相（国内）		5.3.5.1.01-S 5.3.5.1.02-S 5.3.5.1-17-S
	長期（海外）		5.3.5.1.07-S 5.3.5.1.08-S 5.3.5.1.15-S
	長期（国内）		5.3.5.2.02-S 5.3.5.2.03-S 5.3.5.2.10-S 5.3.5.2.11-S
双極性障害患者	第 3 相（国内）		5.3.5.1.01-B
	第 3 相（海外）		5.3.5.1.02-B 5.3.5.1.03-B
	長期（国内）		5.3.5.1.05-B 5.3.5.2.01-B

ルラシドン塩酸塩
製造販売承認申請
CTD 第 1 部

1.6　外国における使用状況等に関する資料

大日本住友製薬株式会社

1. 外国における承認・販売状況

本剤は、2010 年 10 月に米国、2014 年 3 月に EU で承認されて以降、2019 年 10 月現在、米国、EU 加盟国、カナダ、スイス及びオーストラリアなど 45 の国又は地域で販売承認を取得しており、主な国又は地域における承認状況を表 1 に示す。これらの国又は地域での販売名は全て「Latuda」である。また、2019 年 10 月現在、[redacted]カ国にて承認申請中である。

表 1　主な国におけるルラシドンの承認状況（2019 年 10 月現在）

国名又は地域名	効能・効果	用法・用量	承認年月
米国	成人の統合失調症	40～160 mg/日	2010 年 10 月
	成人の双極 I 型障害うつに対する単剤療法ならびにリチウムまたはバルプロ酸との併用療法	20～120 mg/日	2013 年 6 月
	青年（13 歳から 17 歳）の統合失調症	40～80 mg/日	2017 年 1 月
	小児（10 歳から 17 歳）の双極 I 型障害うつに対する単剤療法	20～80 mg/日	2018 年 3 月
EU	成人（18 歳以上）の統合失調症	37～148* mg/日	2014 年 3 月
カナダ	統合失調症	40～160 mg/日	2012 年 6 月
	双極 I 型障害うつに対する単剤療法ならびにリチウムまたはバルプロ酸との併用療法	20～120 mg/日	2014 年 3 月
	青年（15 歳から 17 歳）の統合失調症	40～80 mg/日	2017 年 7 月
	青年（13 歳から 17 歳）の双極 I 型障害うつに対する単剤療法	20～80 mg/日	2018 年 4 月
スイス	成人（18 歳以上）の統合失調症	40～160 mg/日	2013 年 8 月
	双極 I 型障害うつに対する単剤療法ならびにリチウムまたはバルプロ酸との併用療法	20～60 mg/日	2019 年 9 月
オーストラリア	成人の統合失調症	40～160 mg/日	2014 年 3 月
	青年（13 歳から 17 歳）の統合失調症	40～80 mg/日	2018 年 4 月

*：ルラシドン塩酸塩 40-160 mg に相当するルラシドンフリー体の用量で表記されている。

2. 米国および EU における承認内容の概略

米国における承認内容の概略を表 2 に、EU における承認内容の概略を表 3 に示す。

表 2　米国の承認内容の概略

販売名	LATUDA
初回承認年月	2010 年 10 月
剤型	20 mg 錠、40 mg 錠、60 mg 錠、80 mg 錠、120 mg 錠
効能・効果	LATUDA は、以下の治療を適応とする非定型抗精神病薬である。 - 成人および青年（13～17 歳）の統合失調症 - 成人および小児（10～17 歳）における双極 I 型障害に伴う大

<table>
<tr><td></td><td>うつ病エピソード（双極性障害のうつ症状）に対する単剤療法
- 成人における双極 I 型障害に伴う大うつ病エピソード（双極性障害のうつ症状）に対するリチウムまたはバルプロ酸との併用療法</td></tr>
<tr><td>用法・用量</td><td>LATUDA は食事（350 kcal 以上）とともに服用する。LATUDA を食事とともに服用すると、同剤の吸収が大幅に増加する。

<table>
<tr><th>適応症</th><th>推奨開始用量</th><th>推奨用量</th></tr>
<tr><td>統合失調症 –成人</td><td>40 mg/日</td><td>40 mg～160 mg/日</td></tr>
<tr><td>統合失調症 –青年（13 歳から 17 歳）</td><td>40 mg/日</td><td>40 mg～80 mg/日</td></tr>
<tr><td>双極性障害のうつ症状–成人</td><td>20 mg/日</td><td>20 mg～120 mg/日</td></tr>
<tr><td>双極性障害のうつ症状 -小児（10 歳から 17 歳）</td><td>20 mg/日</td><td>20 mg～80 mg/日</td></tr>
</table>
- 中等度および重度の腎機能障害 : 開始用量は 1 日当たり 20 mg、最大用量は 1 日当たり 80 mg が推奨される。
- 中等度および重度の肝機能障害 : 開始用量は 1 日当たり 20 mg、最大用量は中等度の肝機能障害の場合は 1 日当たり 80 mg、重度の肝機能障害の場合は 1 日当たり 40 mg が推奨される。
- 中等度の CYP3A4 阻害剤（ジルチアゼムなど）の併用 : LATUDA の用量は、元の用量の半分に減量する必要がある。開始用量は 1 日当たり 20 mg、最大用量は 1 日当たり 80 mg が推奨される。
- 中等度の CYP3A4 誘導剤の併用 : LATUDA の増量が必要な場合がある。</td></tr>
<tr><td>禁忌</td><td>- LATUDA または製剤に含まれる成分に対して過敏症の既往歴のある者。
- 強力な CYP3A4 阻害剤（ケトコナゾールなど）の併用。
- 強力な CYP3A4 誘導剤（リファンピシンなど）の併用。</td></tr>
<tr><td>直近の添付文書改訂年月</td><td>2018 年 3 月</td></tr>
</table>

表 3　EU の承認内容の概略

販売名	Latuda
承認年月	2014 年 3 月
剤型※	18.5 mg 錠、37 mg 錠、74 mg 錠
効能・効果	Latuda は 18 歳以上の成人における統合失調症の治療に適応される。
用法・用量※	用量 ルラシドンの推奨開始用量は 37 mg を 1 日 1 回である。初回投与量の調整は必要ない。有効な用量範囲は 37～148 mg を 1 日 1 回投与である。用量を増加する場合、医師の判断に基づき、臨床反応を確認して行う。最大 1 日用量が 148 mg を超えないようにすること。 1 日 1 回 111 mg を超える用量を投与中の患者で、投与を中断して中断期間が 3 日を上回る場合には、1 日 1 回 111 mg で投与を再開し、至適用量まで漸増する。それ以外の用量の患者は漸増の必要はなく、中断前の用量から再開できる。 薬物相互作用による用量調整 中等度 CYP3A4 阻害剤との併用時、ルラシドンの推奨開始用量は 18.5mg で、最大投与量は 1 日 1 回 74mg を超えないこととする。軽度及び中等度 CYP3A4 誘導剤との併用時、ルラシドンの用量調節が必要となる場合がある（4.5 項参照）。強力な CYP3A4 阻害剤および誘導剤については、4.3 項参照。 抗精神病薬間の切り替え 薬剤によって薬力学的および薬物動態プロファイルが異なるため、別の抗精神病薬への切り替えが医学的に適切と考えられる場合には、医師による管理が必要である。 高齢者 腎機能が正常な（クレアチニンクリアランス（CrCl）≥ 80 mL/min）高齢者の推奨用量は、正常腎機能の成人と同じである。ただし、高齢者は腎機能が低下している可能性があるため、腎機能の状態に応じた用量調整が必要となることがある。 高用量のルラシドンを投与した高齢者のデータは限られている。ルラシドン 148 mg を投与した高齢者のデータは存在しない。65 歳以上の患者に対する高用量のルラシドンは慎重に投与すること。 腎機能障害患者 軽度の腎機能障害患者では、ルラシドンの用量調整は必要ない。 中等度の腎機能障害（CrCl ≥ 30、< 50 mL/min）、重度の腎機能障害（CrCL >15、< 30 mL/min）、および末期腎疾患（ESRD）（CrCl < 15 mL/min）の患者では、推奨開始用量は 18.5 mg、最大投与量は 1 日 1 回 74 mg を超えないこととする。予想されるベネフィットが潜在的リスクを上回る場合を除き、ルラシドンを ESRD 患者に使用すべきではない。ESRD 患者に使用する場合は、臨床モニタリングを推奨する。 肝機能障害患者 軽度の肝機能障害患者では、ルラシドンの用量調整は必要ない。

	中等度（Child-Pugh 分類 B）および重度（Child-Pugh 分類 C）の肝機能障害患者においては、用量調節が推奨される。推奨開始用量は 18.5 mg である。中等度の肝機能障害患者では 1 日 1 回 74 mg、重度の肝機能障害患者では 1 日 1 回 37 mg の用量を超えないこと。 小児 18 歳未満の小児におけるルラシドンの安全性および有効性は確認されていない。用法・用量での推奨事項はない。 投与方法 Latuda のフィルムコーティング錠は経口剤であり、1 日 1 回食事中に服用する。 食事なしで服用すると、食事中又は食直後に服用した場合と比較して、ルラシドンへの曝露が有意に減少する。 Latuda 錠は苦味があるため、かまずにそのまま服用すること。飲み忘れを防ぐために、毎日同じ時間帯に服用すること。
禁忌	- 有効成分または Latuda 錠に含有される添加剤に対する過敏症。 - 強力な CYP3A4 阻害剤（例えば、ボセプレビル、クラリスロマイシン、コビシスタット、インジナビル、イトラコナゾール、ケトコナゾール、ネファゾドン、ネルフィナビル、ポサコナゾール、リトナビル、サキナビル、テラプレビル、テリスロマイシン、ボリコナゾール）または強力な CYP3A4 誘導剤［例えば、カルバマゼピン、フェノバルビタール、フェニトイン、リファンピシン、セント・ジョーンズ・ワート（セイヨウオトギリソウ）］との併用投与。
直近の添付文書改訂年月	2019 年 1 月

※EU 添付文書は、ルラシドンフリー体での用量で表記されている。ルラシドンフリー体 18.5 mg、37 mg、74 mg、111 mg、148 mg は、それぞれルラシドン塩酸塩 20 mg、40 mg、80 mg、120 mg、160 mg に相当する。

3. 米国の添付文書

米国における添付文書（2018 年 3 月改訂）の原文及び和文を添付する。

4. EU の添付文書

EU における添付文書（2019 年 1 月改訂）の原文及び和文を添付する。

5. 企業中核データシート（Company Core Data Sheet; CCDS）

最新の CCDS（20[redacted]年[redacted]月改訂）の原文を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information for LATUDA.

LATUDA (lurasidone hydrochloride) tablets, for oral use
Initial U.S. Approval: 2010

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis (5.1).**
- **Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients. Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors. (5.2).**

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

Boxed Warning	3/2018
Indications and Usage (1)	3/2018
Dosage and Administration (2.2)	3/2018
Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.6, 5.7, 5.9, 5.12, 5.11, 5.14)	3/2018

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

LATUDA is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia in adults and adolescents (13 to 17 years) (1, 14.1)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults and pediatric patients (10 to 17 years) as monotherapy (1, 14.2)
- Depressive episode associated with Bipolar I Disorder (bipolar depression) in adults as adjunctive therapy with lithium or valproate (1, 14.2)

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

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA (2.3, 12.3).

Indication	Starting Dose	Recommended Dose
Schizophrenia – adults (2.1)	40 mg per day	40 mg to 160 mg per day
Schizophrenia – adolescents (13 to 17 years) (2.1)	40 mg per day	40 mg to 80 mg per day
Bipolar Depression - adults (2.2)	20 mg per day	20 mg to 120 mg per day
Bipolar Depression – pediatric patients (10 to 17 years) (2.2)	20 mg per day	20 mg to 80 mg per day

- Moderate and Severe Renal Impairment: Recommended starting dose is 20 mg per day, and the maximum recommended dose is 80 mg per day (2.4, 8.6).
- Moderate and Severe Hepatic Impairment: Recommended starting dose is 20 mg per day. The maximum recommended dose is 80 mg per day in moderate hepatic impairment and 40 mg per day in severe hepatic impairment (2.5, 8.7).
- Concomitant Use of a Moderate CYP3A4 inhibitor (e.g., diltiazem):
  - LATUDA dose should be reduced to half of the original dose level. Recommended starting dose is 20 mg per day. Maximum recommended dose is 80 mg per day (2.6, 7.1).
- Concomitant Use of a Moderate CYP3A4 Inducer:
  It may be necessary to increase the dose of LATUDA (2.6, 7.1).

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

Tablets: 20 mg, 40 mg, 60 mg, 80 mg and 120 mg (3)

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

- Known hypersensitivity to LATUDA or any components in the formulation (4).
- Concomitant use with a strong CYP3A4 inhibitor (e.g., ketoconazole) (2.6, 4, 7.1).
- Concomitant use with a strong CYP3A4 inducer (e.g., rifampin) (2.6, 4, 7.1).

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

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) (5.3).
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4).
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.5).
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6).
- Hyperprolactinemia: Prolactin elevations may occur (5.7).
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing LATUDA if a clinically significant decline in WBC occurs in the absence of other causative factors (5.8).
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.9).

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

Commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) were (6.1):

- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea
- Adolescent patients (13-17 years) with schizophrenia: somnolence, nausea, akathisia, EPS (non-akathisia), rhinitis (80mg only), and vomiting
- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Pediatric patients (10-17 years) with bipolar depression: nausea, weight increase, and insomnia.

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Pregnancy: May cause extrapyramidal and or/withdrawal symptoms in neonates with third trimester exposure (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2018

Reference ID: 4228037

FULL PRESCRIBING INFORMATION: CONTENTS*

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INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS BEHAVIORS

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

LATUDA is indicated for:

• Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia *[see Clinical Studies (14.1)]*.

• Monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) *[see Clinical Studies (14.2)]*.

• Adjunctive treatment with lithium or valproate in adult patients with major depressive episode associated with bipolar I disorder (bipolar depression) *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 160 mg per day *[see Clinical Studies (14.1)]*. The maximum recommended dose is 160 mg per day.

Adolescents (13 – 17 years)

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg per day to 80 mg per day *[see Clinical Studies (14.1)]*. The maximum recommended dose is 80 mg per day.

2.2 Depressive Episodes Associated with Bipolar I Disorder

Adults

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 20 mg per day to 120 mg per day as monotherapy or as adjunctive therapy with lithium or valproate *[see Clinical Studies (14.2)]*. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy, on average, compared to the lower dose range (20 to 60 mg per day) *[see Clinical Studies (14.2)]*.

Pediatric Patients (10 – 17 years)

The recommended starting dose of LATUDA is 20 mg given once daily as monotherapy. Initial dose titration is not required. The dose may be increased after one week based on clinical response. LATUDA has been shown to be effective in a dose range of 20 mg per day to 80 mg per day as monotherapy. At the end of the clinical study, most of the patients (67%) received 20 mg or 40 mg once daily *[see Clinical Studies (14.2)]*. The maximum recommended dose is 80 mg per day.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

2.3 Administration Information

LATUDA should be taken with food (at least 350 calories). Administration with food substantially increases the absorption of LATUDA. Administration with food increases the AUC approximately 2-fold and increases the Cmax approximately 3-fold. In the clinical studies, LATUDA was administered with food *[see Clinical Pharmacology (12.3)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.1 and 2.2)]*.

2.4 Dose Modifications for Renal Impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day *[see Use in Specific Populations (8.6)]*.

2.5 Dose Modifications for Hepatic Impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg per day. The dose in moderate hepatic impairment patients should not exceed 80 mg per day and the

dose in severe hepatic impairment patients should not exceed 40 per mg/day *[see Use in Specific Populations (8.7)]*.

2.6 Dose Modifications Due to Drug Interactions of CYP3A4 Inhibitors and CYP3A4 Inducers

Concomitant Use with CYP3A4 Inhibitors

LATUDA should not be used concomitantly with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Contraindications (4)]*.

If LATUDA is being prescribed and a moderate CYP3A4 inhibitor (e.g. diltiazem, atazanavir, erythromycin, fluconazole, verapamil etc.) is added to the therapy, the LATUDA dose should be reduced to half of the original dose level. Similarly, if a moderate CYP3A4 inhibitor is being prescribed and LATUDA is added to the therapy, the recommended starting dose of LATUDA is 20 mg per day, and the maximum recommended dose of LATUDA is 80 mg per day *[see Contraindications (4), Drug Interactions (7.1)]*.

Grapefruit and grapefruit juice should be avoided in patients taking LATUDA, since these may inhibit CYP3A4 and alter LATUDA concentrations [*see Drug Interactions (7.1)*].

Concomitant Use with CYP3A4 Inducers

LATUDA should not be used concomitantly with a strong CYP3A4 inducer (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Contraindications (4); Drug Interactions (7.1)]*. If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose after chronic treatment (7 days or more) with the CYP3A4 inducer.

3 DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing.

Table 1: LATUDA Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
20 mg	white to off-white round	L20
40 mg	white to off-white round	L40
60 mg	white to off-white oblong	L60
80 mg	pale green oval	L80
120 mg	white to off-white oval	L120

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.1)]*.

- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Drug Interactions (7.1)]*.
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

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 antidepressant drug effect on suicide.

Table 2: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue LATUDA and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 3.

Table 3: Change in Fasting Glucose in Adult Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
Mean Change from Baseline (mg/dL)						
	n=680	**n=71**	**n=478**	**n=508**	**n=283**	**n=113**
Serum Glucose	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL						
Serum Glucose (≥ 126 mg/dL)	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/260)	5.6% (6/108)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Adolescents

In studies of adolescents and adults with schizophrenia, changes in fasting glucose were similar. In the short-term, placebo-controlled study of adolescents, fasting serum glucose mean values were -1.3 mg/dL for placebo (n=95), +0.1 mg/dL for 40 mg/day (n=90), and +1.8 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 4.

Table 4: Change in Fasting Glucose in the Adult Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
Mean Change from Baseline (mg/dL)			
	n=148	**n=140**	**n=143**
Serum Glucose	+1.8	-0.8	+1.8
Proportion of Patients with Shifts to ≥ 126 mg/dL			
Serum Glucose (≥ 126 mg/dL)	4.3% (6/141)	2.2% (3/138)	6.4% (9/141)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 5.

Table 5: Change in Fasting Glucose in the Adult Adjunctive Therapy Bipolar Depression Studies

	Placebo	LATUDA 20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=302	**n=319**
Serum Glucose	-0.9	+1.2
Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	1.0% (3/290)	1.3% (4/316)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Pediatric Patients (10 to 17 years)

In studies of pediatric patients 10 to 17 years and adults with bipolar depression, changes in fasting glucose were similar. In the 6-week, placebo-controlled study of pediatric patients with bipolar depression, mean change in fasting glucose was +1.6 mg/dL for LATUDA 20 to 80 mg/day (n=145) and -0.5 mg/dL for placebo (n=145).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies

Table 6: Change in Fasting Lipids in Adult Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
Mean Change from Baseline (mg/dL)						
	n=660	**n=71**	**n=466**	**n=499**	**n=268**	**n=115**
Total Cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Adolescents

In the adolescent short-term, placebo-controlled study, fasting serum cholesterol mean values were -9.6 mg/dL for placebo (n=95), -4.4 mg/dL for 40 mg/day (n=89), and +1.6 mg/dL for 80 mg/day (n=92), and fasting serum triglyceride mean values were +0.1 mg/dL for placebo (n=95), -0.6 mg/dL for 40 mg/day (n=89), and +8.5 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 7.

Table 7: Change in Fasting Lipids in the Adult Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
Mean Change from Baseline (mg/dL)			
	n=147	**n=140**	**n=144**
Total cholesterol	-3.2	+1.2	-4.6
Triglycerides	+6.0	+5.6	+0.4
Proportion of Patients with Shifts			
Total cholesterol (≥ 240 mg/dL)	4.2% (5/118)	4.4% (5/113)	4.4% (5/114)
Triglycerides (≥ 200 mg/dL)	4.8% (6/126)	10.1% (12/119)	9.8% (12/122)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 mg/dL (n=130) and -1.0 mg/dL (n=130) at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in Table 8.

Table 8: Change in Fasting Lipids in the Adult Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	**20 to 120 mg/day**
Mean Change from Baseline (mg/dL)		
	n=303	**n=321**
Total cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6
Proportion of Patients with Shifts		
Total cholesterol (≥ 240 mg/dL)	5.7% (15/263)	5.4% (15/276)
Triglycerides (≥ 200 mg/dL)	8.6% (21/243)	10.8% (28/260)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and +5.3 (n=88) mg/dL at week 24, respectively.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, mean change in fasting cholesterol was -6.3 mg/dL for LATUDA 20 to 80 mg/day (n=144) and -1.4 mg/dL for placebo (n=145), and mean change in fasting triglyceride was -7.6 mg/dL for LATUDA 20 to 80 mg/day (n=144) and +5.9 mg/dL for placebo (n=145).

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Adults

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 9. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 *[see Clinical Studies (14.1)]*, respectively. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients and 3.3% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in Adult Schizophrenia Studies

		LATUDA				
	Placebo (n=696)	**20 mg/day (n=71)**	**40 mg/day (n=484)**	**80 mg/day (n=526)**	**120 mg/day (n=291)**	**160 mg/day (n=114)**
All Patients	-0.02	-0.15	+0.22	+0.54	+0.68	+0.60

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Adolescents

Data from the short-term, placebo-controlled adolescent schizophrenia study are presented in Table 10. The mean change in weight gain was +0.5 kg for LATUDA-treated patients compared to +0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.3% for LATUDA-treated patients and 4.5% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adolescent Schizophrenia Study

		LATUDA	
	Placebo (n=111)	**40 mg/day (n=109)**	**80 mg/day (n=104)**
All Patients	+0.2	+0.3	+0.7

Bipolar Depression

Adults

Monotherapy

Data from the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 11. The mean change in weight gain was +0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients and 0.7% for placebo-treated patients.

Table 11: Mean Change in Weight (kg) from Baseline in the Adult Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo (n=151)	**20 to 60 mg/day (n=143)**	**80 to 120 mg/day (n=147)**
All Patients	-0.04	+0.56	+0.02

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 12. The mean change in weight gain was +0.11 kg for LATUDA-treated patients compared to +0.16 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients and 0.3% for placebo-treated patients.

Table 12: Mean Change in Weight (kg) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo (n=307)	**20 to 120 mg/day (n=327)**
All Patients	+0.16	+0.11

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

Pediatric Patients (10 to 17 years)

Data from the 6-week, placebo-controlled bipolar depression study in patients 10 to 17 years are presented in Table 13. The mean change in weight gain was +0.7 kg for LATUDA-treated patients compared to +0.5 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.0% for LATUDA-treated patients and 5.3% for placebo-treated patients.

Table 13: Mean Change in Weight (kg) from Baseline in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

		LATUDA
	Placebo (n=170)	**20 to 80 mg/day (n=175)**
All Patients	+0.5	+0.7

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients *[see Adverse Reactions (0)]*.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a carcinogenicity study conducted with lurasidone in rats and mice *[see Nonclinical Toxicology (13)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 14.

Table 14: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

		LATUDA				
	Placebo	**20 mg/day**	**40 mg/day**	**80 mg/day**	**120 mg/day**	**160 mg/day**
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	+3.3 (n=284)	+3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	+6.7 (n=70)	+7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	+3.1 (n=214)	+2.4 (n=79)

The proportion of patients with prolactin elevations ≥5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients and = 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 5.7% for LATUDA-treated patients and = 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 1.6% and 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.1 ng/mL and was +0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +1.0 ng/mL and for females was +2.6 ng/mL. Median changes for prolactin by dose are shown in Table 15.

Table 15: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Study

	Placebo	**LATUDA 40 mg/day**	**LATUDA 80 mg/day**
All Patients	+0.10 (n=103)	+0.75 (n=102)	+1.20 (n=99)
Females	+0.70 (n=39)	+0.60 (n=42)	+4.40 (n=33)
Males	0.00 (n=64)	+0.75 (n=60)	+1.00 (n=66)

The proportion of patients with prolactin elevations ≥5x ULN was 0.5% for LATUDA-treated patients and 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 1.3% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA treated patients and 1.6% for placebo-treated male patients.

Bipolar Depression

Adults

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 16.

Table 16: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
All Patients	+0.3 (n=147)	+1.7 (n=140)	+3.5 (n=144)
Females	0.0 (n=82)	+1.8 (n=78)	+5.3 (n=88)
Males	+0.4 (n=65)	+1.2 (n=62)	+1.9 (n=56)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo

The proportion of patients with prolactin elevations ≥5x upper limit of normal (ULN) was 0.4% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% and 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA as monotherapy in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 17.

Table 17: Median Change in Prolactin (ng/mL) from Baseline in the Adult Adjunctive Therapy Bipolar Depression Studies

	Placebo	LATUDA 20 to 120 mg/day
All Patients	0.0 (n=301)	+2.8 (n=321)
Females	+0.4 (n=156)	+3.2 (n=162)
Males	-0.1 (n=145)	+2.4 (n=159)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% and 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.10 ng/mL and was +0.50 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +0.85 ng/mL and for females was +2.50 ng/mL. Median changes for prolactin are shown in Table 18.

Table 18: Median Change in Prolactin (ng/mL) from Baseline in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

	Placebo	LATUDA 20 to 80 mg/day
All Patients	+0.50 (n=157)	+1.10 (n=165)
Females	+0.55 (n=78)	+2.50 (n=83)
Males	+0.50 (n=79)	+0.85 (n=82)

The proportion of patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients and 0.6% for placebo-treated patients. The proportion of female patients with prolactin

elevations ≥5x ULN was 0% for LATUDA-treated patients and 1.3% for placebo-treated female patients. No male patients in the placebo or LATUDA treatment groups had prolactin elevations ≥5x ULN.

5.8 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia

Adults

The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Adolescents

The incidence of orthostatic hypotension reported as adverse events from the short-term, placebo-controlled adolescent schizophrenia study was 0.5% (1/214) in LATUDA-treated patients and 0% (0/112) in placebo-treated patients. No syncope event was reported.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0% with LATUDA 40 mg and 2.9% with LATUDA 80 mg, compared to 1.8% with placebo.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, there were no reported adverse events of orthostatic hypotension or syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 80 mg/day, compared to 0.6% with placebo.

5.10 Falls

Latuda may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Schizophrenia

In adult short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.

Bipolar Depression

Monotherapy

In the adult and pediatric 6-week, flexible-dose, placebo-controlled monotherapy bipolar depression studies, no patients experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

5.12 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia

Adults

In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, somnolence was reported by 14.5% (31/214) of patients treated with LATUDA (15.5% LATUDA 40 mg and 13.5% LATUDA 80 mg,/day) compared to 7.1% (8/112) of placebo patients.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 80 to120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, somnolence was reported by 11.4% (20/175) of patients treated with LATUDA 20 to 80 mg/day compared to 5.8% (10/172) of placebo treated patients.

5.13 Body Temperature Dysregulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.14 Activation of Mania/Hypomania

Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the adult bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (03)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.13)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

Adults

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 adult patients exposed to one or more doses of LATUDA for the treatment of schizophrenia, and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of

the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia

The following findings are based on the short-term, placebo-controlled premarketing adult studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 19**.**

Table 19: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Adult Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction						
		LATUDA					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All LATUDA (N=1508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Somnolence*	7	15	16	15	26	8	17
Akathisia	3	6	11	12	22	7	13
Extrapyramidal Disorder**	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

	Percentage of Patients Reporting Reaction						
		LATUDA					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All LATUDA (N=1508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

** Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the adult short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5%, in either dose group, and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 20.

Table 20: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adult Short-term Monotherapy Bipolar Depression Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=168) (%)**	**LATUDA 20-60 mg/day (N=164) (%)**	**LATUDA 80-120 mg/day (N=167) (%)**	**All LATUDA (N=331) (%)**
Gastrointestinal Disorders				
Nausea	8	10	17	14
Dry Mouth	4	6	4	5
Vomiting	2	2	6	4
Diarrhea	2	5	3	4
Infections and Infestations				
Nasopharyngitis	1	4	4	4
Influenza	1	<1	2	2
Urinary Tract Infection	<1	2	1	2
Musculoskeletal and Connective Tissue Disorders				
Back Pain	<1	3	<1	2
Nervous System Disorders				
Extrapyramidal Symptoms*	2	5	9	7
Akathisia	2	8	11	9
Somnolence**	7	7	14	11
Psychiatric Disorders				
Anxiety	1	4	5	4

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:

In the adult short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [*see Clinical Studies (14.2)*] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

The following findings are based on two adult short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 21.

Table 21: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adult Short-term Adjunctive Therapy Bipolar Depression Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=334) (%)**	**LATUDA 20 to 120 mg/day (N=360) (%)**
Gastrointestinal Disorders		
Nausea	10	14
Vomiting	1	4
General Disorders		
Fatigue	1	3
Infections and Infestations		
Nasopharyngitis	2	4
Investigations		
Weight Increased	<1	3
Metabolism and Nutrition Disorders		
Increased Appetite	1	3
Nervous System Disorders		
Extrapyramidal Symptoms*	9	14
Somnolence**	5	11
Akathisia	5	11
Psychiatric Disorders		
Restlessness	<1	4

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

** Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Adolescents

Schizophrenia

The following findings are based on the short-term, placebo-controlled adolescent study for schizophrenia in which LATUDA was administered at daily doses ranging from 40 (N=110) to 80 mg (N=104).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in adolescent patients (13 to 17 years) treated with LATUDA were somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia, 40mg only), vomiting, and rhinorrhea/rhinitis (80mg only).

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated adolescent patients (13 to 17 years) was 4% and 8%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in adolescent patients with schizophrenia) are shown in Table 22.

Table 22: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adolescent Short-term Schizophrenia Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=112)**	**LATUDA 40 mg/day (N=110)**	**LATUDA 80 mg/day (N=104)**	**All LATUDA (N=214)**
Gastrointestinal Disorders				
Nausea	3	13	14	14
Vomiting	2	8	6	8
Diarrhea	1	3	5	4
Dry Mouth	0	2	3	2
Infections and Infestations				
Viral Infection**	6	11	10	10
Rhinitis***	2	<1	8	4
Oropharyngeal pain	0	<1	3	2
Tachycardia	0	0	3	1
Nervous System Disorders				
Somnolence*	7	15	13	15
Akathisia	2	9	9	9
Dizziness	1	5	5	5

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=112)**	**LATUDA 40 mg/day (N=110)**	**LATUDA 80 mg/day (N=104)**	**All LATUDA (N=214)**

Note: Figures rounded to the nearest integer

* Somnolence includes adverse event terms: hypersomnia, sedation, and somnolence

** Viral Infection includes adverse event terms: nasopharyngitis, influenza, viral infection, upper respiratory tract infection

*** Rhinitis incudes adverse event terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion

Reference ID: 4228037

Pediatric Patients (10 to 17 years)

Bipolar Depression

The following findings are based on the 6-week , placebo-controlled study for bipolar depression in pediatric patients 10 to 17 years in which LATUDA was administered at daily doses ranging from 20 to 80 mg (N=175).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥5%, and at least twice the rate of placebo) in pediatric patients (10 to 17 years) treated with LATUDA were nausea, weight increase, and insomnia.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated pediatric patients 10 to 17 years was 2% and 2%, respectively.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in pediatric patients with bipolar depression) are shown in Table 23.

Table 23: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the 6-Week Bipolar Depression Study in Pediatric Patients (10 to 17 years)

	Percentage of Patients Reporting Reaction	
Body System or Organ Class **Dictionary-derived Term**	**Placebo** **(N=172)**	**LATUDA** **20 to 80 mg/day** **(N=175)**
Gastrointestinal Disorders		
Nausea	6	16
Vomiting	4	6
Abdominal Pain Upper	2	3
Diarrhea	2	3
Abdominal Pain	1	3
General Disorders And Administration Site Conditions		
Fatigue	2	3
Investigations		
Weight Increased	2	7
Metabolism and Nutrition Disorders		
Decreased Appetite	2	4
Nervous System Disorders		
Somnolence*	6	11
Extrapyramidal symptoms**	5	6
Dizziness	5	6
Psychiatric Disorders		
Insomnia	2	5
Abnormal Dreams	2	2
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal Pain	2	2

Note: Figures rounded to the nearest integer

*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

**EPS includes adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor

Extrapyramidal Symptoms

Schizophrenia

Adults

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% and 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% and 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 24.

Table 24: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

		LATUDA				
Adverse Event Term	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adolescents

In the short-term, placebo-controlled, study of schizophrenia in adolescents, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was higher in the 40 mg (10%) and the 80 mg (7.7%) treatment groups vs. placebo (3.6%); and the incidence of akathisia-related events for LATUDA-treated patients was 8.9% vs. 1.8% for placebo-treated patients. Incidence of EPS by dose is provided in Table 25.

Table 25: Incidence of EPS Compared to Placebo in the Adolescent Schizophrenia Study

		LATUDA	
Adverse Event Term	**Placebo (N=112) (%)**	**40 mg/day (N=110) (%)**	**80 mg/day (N=104) (%)**
All EPS events	**5**	**14**	**14**
All EPS events, excluding Akathisia/Restlessness	**4**	**7**	**7**
Akathisia	2	9	9
Parkinsonism**	<1	4	0
Dyskinesia	<1	<1	1
Dystonia*	0	<1	1

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, trismus, oculogyric crisis, oromandibular dystonia, tongue spasm, and torticollis
** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation

Bipolar Depression

Adults

Monotherapy

In the adult short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% and 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% and 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 26.

Table 26: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

Adverse Event Term	Placebo (N=168) (%)	LATUDA 20 to 60 mg/day (N=164) (%)	LATUDA 80 to 120 mg/day (N=167) (%)
All EPS events	**5**	**12**	**20**
All EPS events, excluding Akathisia/Restlessness	**2**	**5**	**9**
Akathisia	2	8	11
Dystonia*	0	0	2
Parkinsonism**	2	5	8
Restlessness	<1	0	3

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 13.9% and 8.7% for placebo. The incidence of akathisia for LATUDA-treated patients was 10.8% and 4.8% for placebo-treated patients. Incidence of EPS is provided in Table 27.

Table 27: Incidence of EPS Compared to Placebo in the Adult Adjunctive Therapy Bipolar Depression Studies

Adverse Event Term	Placebo (N=334) (%)	LATUDA 20 to 120 mg/day (N=360) (%)
All EPS events	**13**	**24**
All EPS events, excluding Akathisia/Restlessness	**9**	**14**
Akathisia	5	11
Dystonia*	<1	1
Parkinsonism**	8	13
Restlessness	<1	4

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled study of bipolar depression in pediatric patients 10 to 17 years, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was similar in the LATUDA 20 to 80 mg/day (3.4%) treatment group vs. placebo (3.5%); and the incidence of akathisia-related events for LATUDA-treated patients was 2.9% vs. 3.5% for placebo-treated patients. Incidence of EPS by dose is provided in Table 28.

Table 28: Incidence of EPS Compared to Placebo in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

Adverse Event Term	Placebo (N=172) (%)	LATUDA 20 to 80 mg/day (N=175) (%)
All EPS events*	**5**	**6**
All EPS events, excluding Akathisia/Restlessness	**4**	**3**
Akathisia	4	3
Parkinsonism**	<1	<1
Dystonia***	1	<1
Salivary hypersecretion	<1	<1
Psychomotor hyperactivity	0	<1
Tardive Dyskinesia	<1	0

Note: Figures rounded to the nearest integer
* EPS include adverse event terms: akathisia, cogwheel rigidity, dyskinesia, dystonia, hyperkinesia, joint stiffness, muscle rigidity, muscle spasms, musculoskeletal stiffness, oculogyric crisis, parkinsonism, tardive dyskinesia, and tremor
** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation
***Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

Schizophrenia

Adults

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Adolescents

The mean change from baseline for LATUDA- treated patients with adolescent schizophrenia for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 7.0%; placebo, 1.8%), the SAS (LATUDA, 8.3%; placebo, 2.7%) and the AIMS (LATUDA, 2.8%; placebo, 0.9%).

Bipolar Depression

Adults

Monotherapy

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Pediatric Patients (10 to 17 years)

The mean change from baseline for LATUDA- treated pediatric patients 10 to 17 years with bipolar depression for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients and placebo for the BAS (LATUDA, 4.6%; placebo, 2.4%), the SAS (LATUDA, 0.6%; placebo, 0%) and was the same for the AIMS (LATUDA, 0%; placebo, 0%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia

Adults

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Adolescents

In the short-term, placebo-controlled, adolescent schizophrenia study, dystonia occurred in 1% of LATUDA-treated patients (1% LATUDA 40 mg and 1% LATUDA 80 mg) compared to 0% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Bipolar Depression

Adults

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, dystonia occurred in 0.6% of LATUDA-treated patients compared to 1.2% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by adult patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in

Table 19 or those that appear elsewhere in the LATUDA label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye Disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis*

General Disorders and Administrative Site Conditions: ***Rare:*** *sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolism and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *cerebrovascular accident, dysarthria*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Frequent:*** *hypertension*

Clinical Laboratory Changes

Schizophrenia

Adults

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 29).

Table 29: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adult Schizophrenia Studies

Laboratory Parameter	Placebo (N=708)	LATUDA 20 mg/day (N=71)	LATUDA 40 mg/day (N=487)	LATUDA 80 mg/day (N=538)	LATUDA 120 mg/day (N=291)	LATUDA 160 mg/day (N=121)
Serum Creatinine Elevated	2%	1%	2%	2%	5%	7%

Adolescents

Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was –0.009 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo (Table 30).

Table 30: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adolescent Schizophrenia Study

Laboratory Parameter	Placebo (N=103)	LATUDA 40 mg/day (N=97)	LATUDA 80 mg/day (N=97)
Serum Creatinine Elevated	2.9%	7.2%	7.2%

Bipolar Depression

Adults

Monotherapy

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 31).

Table 31: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

Laboratory Parameter	Placebo (N=168)	LATUDA 20 to 60 mg/day (N=164)	LATUDA 80 to 120 mg/day (N=167)
Serum Creatinine Elevated	<1%	2%	4%

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive–studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 32).

Table 32: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies

Laboratory Parameter	Placebo (N=334)	LATUDA 20 to 120 mg/day (N=360)
Serum Creatinine Elevated	2%	4%

Pediatric Patients (10 to 17 years)

Serum Creatinine: In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, the mean change from Baseline in serum creatinine was +0.021 mg/dL for LATUDA-treated patients compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 6.7% (11/163) of LATUDA-treated patients and 4.5% (7/155) on placebo (Table 33).

Table 33: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

Laboratory Parameter	Placebo (N=155)	LATUDA 20 to 80 mg/day (N=163)
Serum Creatinine Elevated	4.5%	6.7%

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Latuda. 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.

Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, dyspnea, and rash.

Metabolism and Nutrition Disorders: Hyponatremia

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with LATUDA

Table 34: Clinically Important Drug Interactions with Latuda

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of LATUDA with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [*see Clinical Pharmacology (12.3)*].
Intervention:	LATUDA should not be used concomitantly with strong CYP3A4 inhibitors [*see Contraindications (4)*].
Examples:	Ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil
Moderate CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of LATUDA with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone [*see Clinical Pharmacology (12.3)*].
Intervention:	LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 [*see Dosage and Administration (2.6)*].
Examples:	Diltiazem, atazanavir, erythromycin, fluconazole, verapamil
Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [*see Clinical Pharmacology (12.3)*].
Intervention:	LATUDA should not be used concomitantly with strong CYP3A4 inducers [*see Contraindications (4)*].
Examples:	Rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine
Moderate CYP3A4 Inducers	
Clinical Impact:	Concomitant use of LATUDA with moderate CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone [*see Clinical Pharmacology (12.3)*].
Intervention:	LATUDA dose should be increased when used concomitantly with moderate inducers of CYP3A4 [*see Dosage and Administration (2.6)*].
Examples:	Bosentan, efavirenz, etravirine, modafinil, nafcillin

7.2 Drugs Having No Clinically Important Interactions with LATUDA

Based on pharmacokinetic studies, no dosage adjustment of LATUDA is required when administered concomitantly with lithium, valproate, or substrates of P-gp or CYP3A4 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *[see Clinical Considerations]*. There are no studies of LATUDA use in pregnant women. The limited available data are not sufficient to inform a drug-associated risk of birth defects or miscarriage. In animal reproduction studies, no teratogenic effects were seen in pregnant rats and rabbits given lurasidone during the period of organogenesis at doses approximately 1.5- and 6-times, the maximum recommended human dose (MRHD) of 160 mg/day, respectively based on mg/m^2 body surface area *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Pregnant rats were treated with oral lurasidone at doses of 3, 10, and 25 mg/kg/day during the period of organogenesis. These doses are 0.2, 0.6, and 1.5 times the MRHD of 160 mg/day based on mg/m^2 body surface area. No teratogenic or embryo-fetal effects were observed up to 1.5 times the MHRD of 160 mg/day, based on mg/m^2 .

Pregnant rabbits were treated with oral lurasidone at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m^2. No teratogenic or embryo-fetal effects were observed up to 6 times the MHRD of 160 mg/day based on mg/m^2.

Pregnant rats were treated with oral lurasidone at doses of 0.4, 2, and 10 mg/kg/day during the periods of organogenesis and lactation. These doses are 0.02, 0.1 and 0.6 times the MRHD of 160 mg/day based on mg/m^2. No pre- and postnatal developmental effects were observed up to 0.6 times the MRHD of 160 mg/day, based on mg/m^2.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of lurasidone in human milk, the effects on the breastfed infant, or the effects on milk production. Lurasidone is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for LATUDA and any potential adverse effects on the breastfed infant from LATUDA or from the underlying maternal condition.

8.4 Pediatric Use

Schizophrenia

The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients *[see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]*.

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with schizophrenia.

Bipolar Depression

The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

The safety and effectiveness of LATUDA has not been established in pediatric patients less than 10 years of age with bipolar depression.

Irritability Associated with Autistic Disorder

The effectiveness of LATUDA in pediatric patients for the treatment of irritability associated with autistic disorder has not been established.

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision [DSM-IV-TR] criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 20mg, 14/51 or 27% for 60mg, and 2/49 or 4% for placebo), particularly in children ages 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

Juvenile animal studies

Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m^2. Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose

(MRHD) of 160 mg/day based on mg/m^2. The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m^2. In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased serum estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m^2. Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m^2 and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atretic follicles at doses as low as 0.2 times the MRHD based on mg/m^2. Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MHRD based on mg/m^2 and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m^2.

8.5 Geriatric Use

Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1, 5.3)]*.

8.6 Renal Impairment

Reduce the maximum recommended dosage in patients with moderate or severe renal impairment (CLcr<50 mL/minute). Patients with impaired renal function (CLcr<50 mL/minute) had higher exposure to lurasidone than patients with normal renal function [*see Clinical Pharmacology (12.3)*]. Greater exposure may increase the risk of LATUDA-associated adverse reactions [*see Dosage and Administration (2.4)*]

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to lurasidone than patients with normal hepatic function [*see Clinical Pharmacology (12.3)*]. Greater exposure may increase the risk of LATUDA-associated adverse reactions [*see Dosage and Administration (2.5)*].

8.8 Other Specific Populations

No dosage adjustment for LATUDA is required on the basis of a patient's sex, race, or smoking status *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LATUDA is not a controlled substance.

9.2 Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

No specific antidotes for LATUDA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

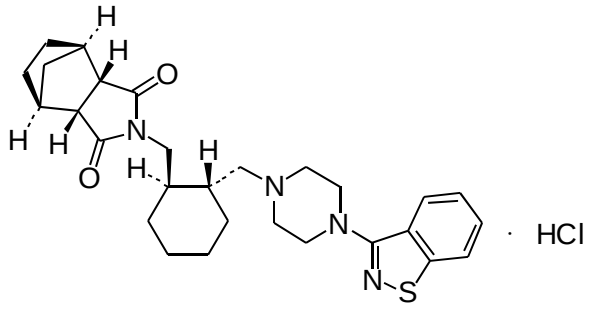
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11 DESCRIPTION

LATUDA is an atypical antipsychotic belonging to the chemical class of benzisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S \cdot HCl$ and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 20 mg, 40 mg, 60 mg, 80 mg, or 120 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of lurasidone in the treatment of schizophrenia and bipolar depression is unclear. However, its efficacy in schizophrenia and bipolar depression could be mediated through a combination of central dopamine D_2 and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

Lurasidone is an antagonist with high affinity binding at the dopamine D_2 receptors (Ki of 1 nM) and the serotonin 5-HT_{2A} (Ki of 0.5 nM) and 5-HT_7 (Ki of 0.5 nM) receptors. It also binds with moderate affinity to the human α_{2C} adrenergic receptors (Ki of 11 nM), is a partial agonist at serotonin 5-HT_{1A} (Ki of 6.4 nM) receptors, and is an antagonist at the α_{2A} adrenergic receptors (Ki of 41 nM). Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} > 1,000 nM).

ECG Changes

The effects of LATUDA on the QTc interval were evaluated in a randomized, double-blind, multiple-dose, parallel-dedicated thorough QT study in 43 patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily and completed the study. The maximum mean (upper 1-sided, 95% CI) increase in baseline-adjusted QTc intervals based on individual correction method (QTcI) was 7.5 (11.7) ms and 4.6 (9.5) ms, for the 120 mg and 600 mg dose groups respectively, observed at 2 to 4 hours after dosing. In this study, there was no apparent dose (exposure)-response relationship.

In short-term, placebo-controlled studies in schizophrenia and bipolar depression, no post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA or placebo.

12.3 Pharmacokinetics

Adults

The activity of LATUDA is primarily due to the parent drug. The pharmacokinetics of LATUDA is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of LATUDA are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: LATUDA is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. LATUDA is highly bound (~99%) to serum proteins.

In a food effect study, LATUDA mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. LATUDA exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content *[*see *Dosage and Administration (2.3)]*.

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food *[see Dosage and Administration (2.3)]*.

Metabolism and Elimination: LATUDA is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. LATUDA is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220). Based on *in vitro* studies, LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. Because LATUDA is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of LATUDA.

Transporter proteins: In vitro studies suggest LATUDA is not a substrate of OATP1B1 or OATP1B3, however, is probably a substrate of P-gp and BCRP. *In vitro* studies indicate that LATUDA is not expected to inhibit transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K and BSEP at clinically relevant concentrations. LATUDA is not a clinically significant inhibitor of P-gp. However, it may inhibit BCRP.

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [^{14}C]-labeled LATUDA.

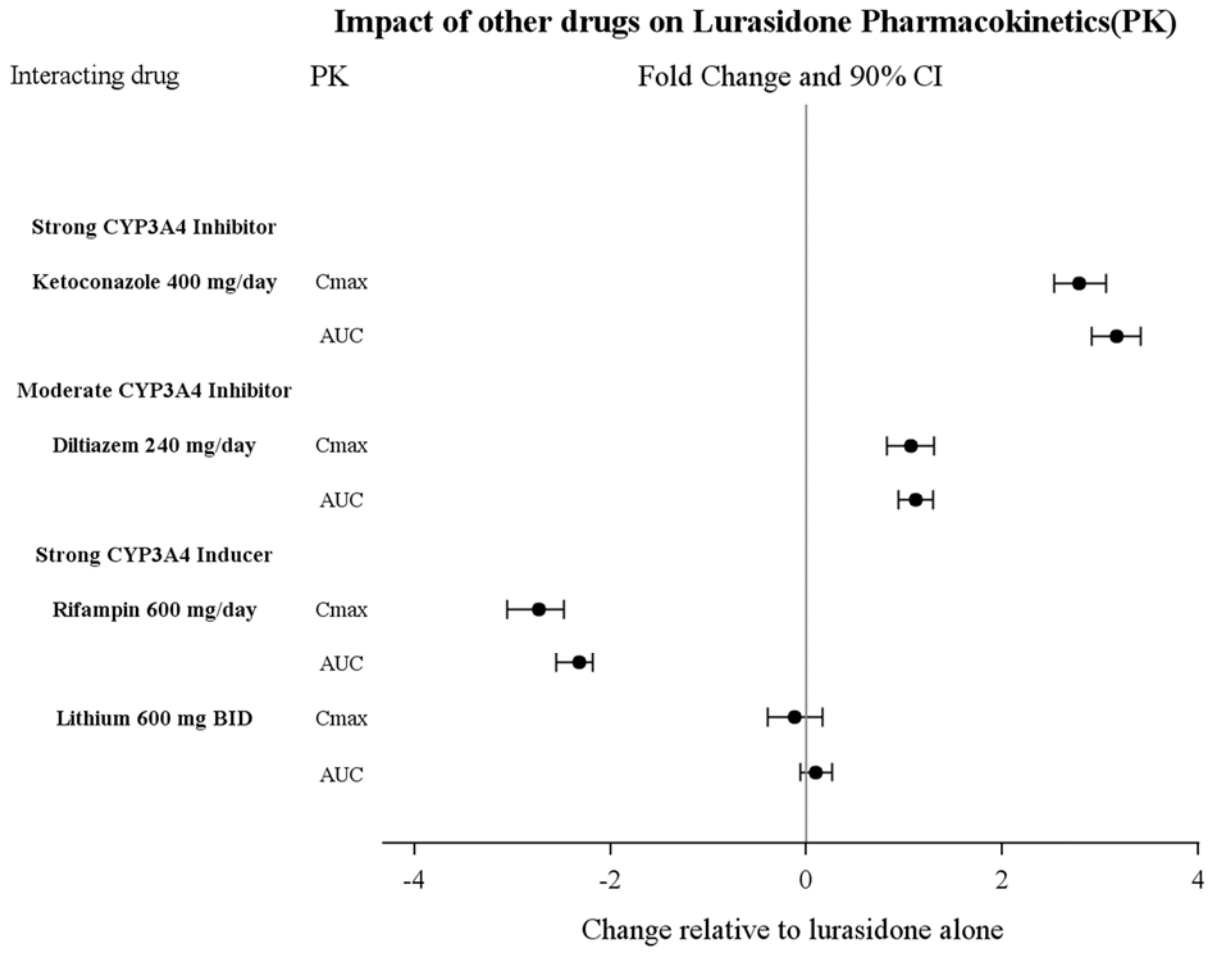
Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

Drug Interaction Studies

Effects of other drugs on the exposure of lurasidone are summarized in Figure 1. A population PK analyses concluded that coadministration of lithium 300-2400 mg/day or valproate 300-2000 mg/day with lurasidone for up to 6 weeks has minimal effect on lurasidone exposure.

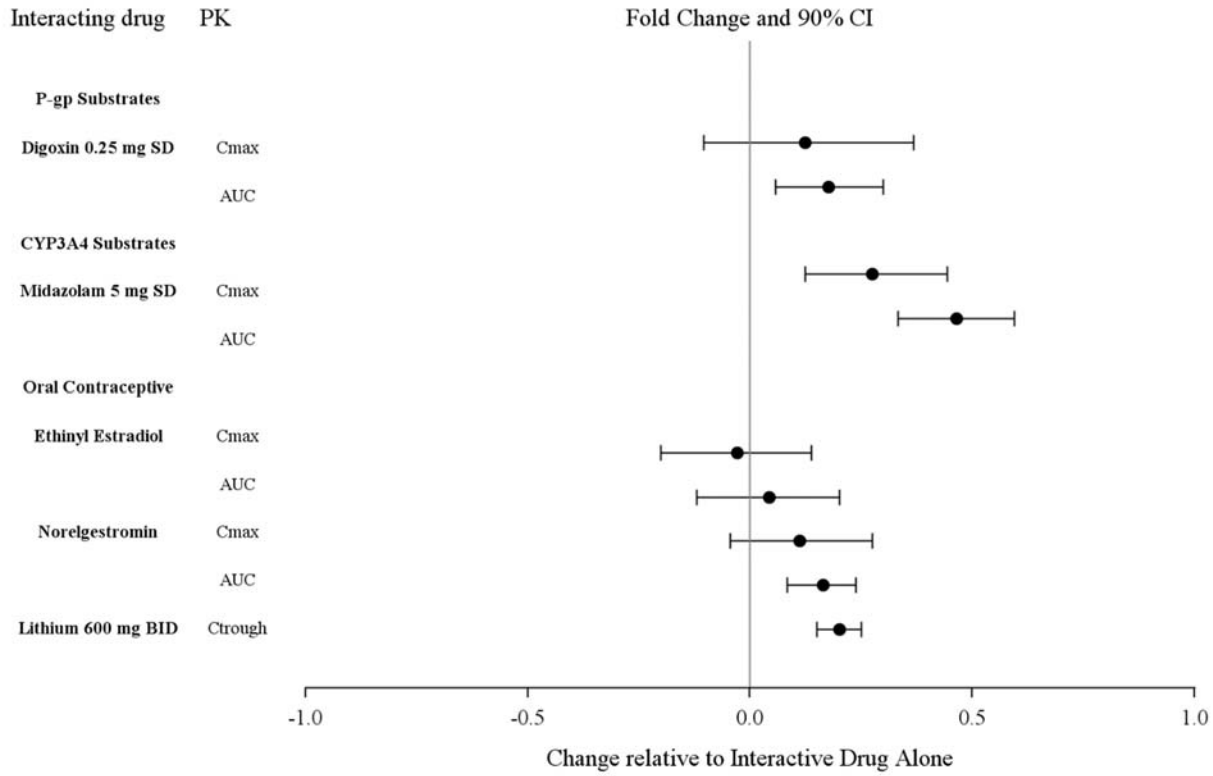
And the effects of LATUDA on the exposures of other drugs are summarized in Figure 2. A population PK analyses concluded that coadministration of lurasidone has minimal effect on lithium and valproate exposure when it is coadministered with lithium 300-2400 mg/day or valproate 300-2000 mg/day.

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



Reference ID: 4228037

Figure 2: Impact of LATUDA on Other Drugs



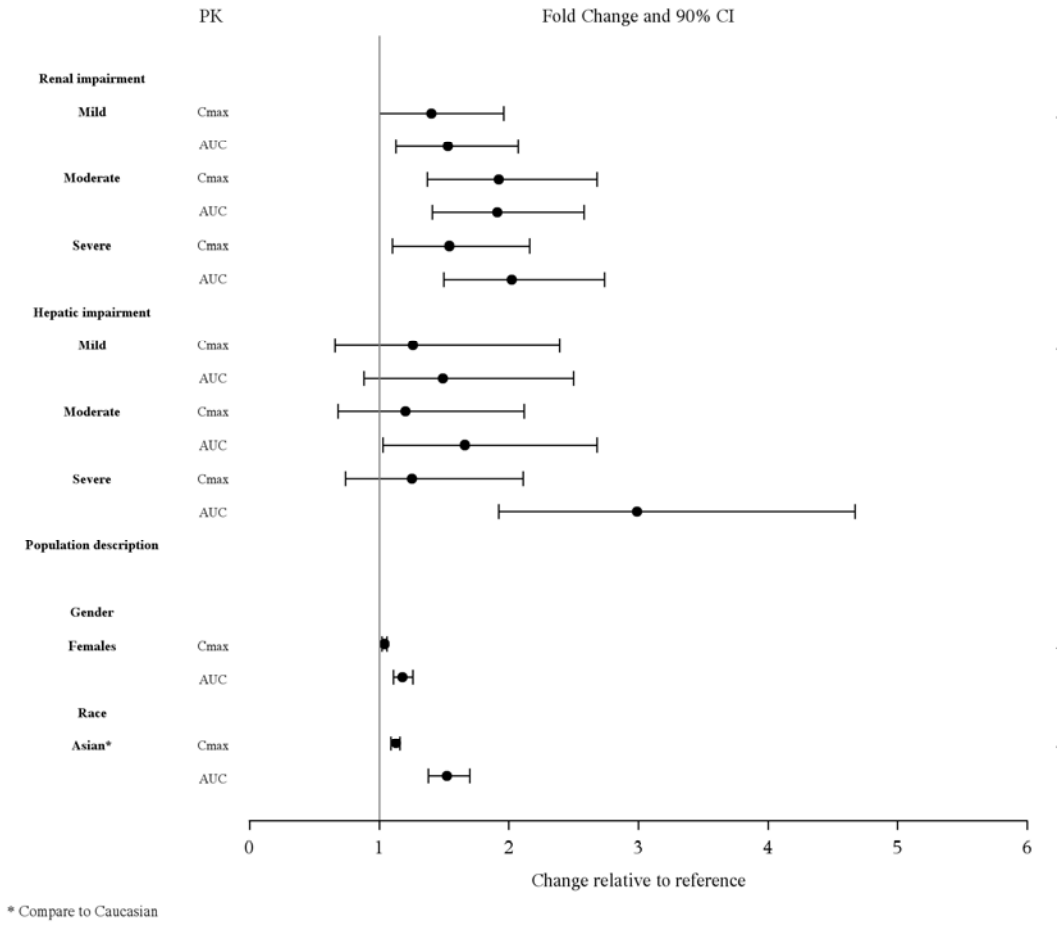
Studies in Specific Populations

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Pediatric Patients

LATUDA exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to that in adults across the dose range from 40 to 160 mg, without adjusting for body weight.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lurasidone increased incidences of malignant mammary gland tumors and pituitary gland adenomas in female mice orally dosed with 30, 100, 300, or 650 mg/kg/day. The lowest dose produced plasma levels (AUC) approximately equal to those in humans receiving the MRHD of 160 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 14 times those in humans receiving the MRHD.

Lurasidone increased the incidence of mammary gland carcinomas in female rats orally dosed at 12 and 36 mg/kg/day: the lowest dose; 3 mg/kg/day is the no-effect dose which produced plasma levels (AUC) 0.4 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to the highest dose tested, which produced plasma levels (AUC) 6 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin-mediated *[see Warnings and Precautions (5.7)]*.

Mutagenesis: Lurasidone did not cause mutation or chromosomal aberration when tested *in vitro* and *in vivo test battery*. Lurasidone was negative in the Ames gene mutation test, the Chinese Hamster Lung (CHL) cells, and in the *in vivo* mouse bone marrow micronucleus test up to 2000 mg/kg which is 61 times the MRHD of 160 mg/day based on mg/m^2 body surface area.

Impairment of Fertility: Estrus cycle irregularities were seen in rats orally administered lurasidone at 1.5, 15 and 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through gestation day 7. No effect was seen at the lowest dose of 0.1 mg/kg which is approximately 0.006 times the MRHD of 160 mg/day based on mg/m^2. Fertility was reduced only at the highest dose, which was reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was approximately equal to the MRHD based on mg/m^2.

Lurasidone had no effect on fertility in male rats treated orally for 64 consecutive days prior to mating and during the mating period at doses up to 9 times the MRHD based on mg/m^2.

14 CLINICAL STUDIES

14.1 Schizophrenia

Adults

The efficacy of LATUDA for the treatment of schizophrenia was established in five short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.4 years, range 18-72) who met DSM-IV criteria for schizophrenia. An active-control arm (olanzapine or quetiapine extended-release) was included in two studies to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. The BPRSd consists of 18 items rated on a scale of 1 (not present) to 7 (severe). BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a clinician-rated scale that measures the subject's current illness state on a 1- to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

Reference ID: 4228037

The results of the studies follow:

1. Study 1: In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. Study 2: In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. Study 3: In a 6-week, placebo- and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. Study 4: In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.
5. Study 5: In a 6-week, placebo- and active-controlled trial (N=482) involving two fixed doses of LATUDA (80 or 160 mg/day) and an active control (quetiapine extended-release), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80, 120 and 160 mg/day has been established (Table 35).

Table 35: Primary Efficacy Results for Studies in Adult Patients with Schizophrenia (BPRSd or PANSS Scores)

Study	Treatment Group	Primary Efficacy Measure: BPRSd		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
1	LATUDA (40 mg/day)*	54.2 (8.8)	-9.4 (1.6)	-5.6 (-9.8, -1.4)
	LATUDA (120 mg/day)*	52.7 (7.6)	-11.0 (1.6)	-6.7 (-11.0, -2.5)
	Placebo	54.7 (8.1)	-3.8 (1.6)	--
2	LATUDA (80 mg/day)*	55.1 (6.0)	-8.9 (1.3)	-4.7 (-8.3, -1.1)
	Placebo	56.1 (6.8)	-4.2 (1.4)	--
		Primary Efficacy Measure: PANSS		
3	LATUDA (40 mg/day)*	96.6 (10.7)	-25.7 (2.0)	-9.7 (-15.3, -4.1)
	LATUDA (120 mg/day)*	97.9 (11.3)	-23.6 (2.1)	-7.5 (-13.4, -1.7)
	Olanzapine (15 mg/day)*[b]	96.3 (12.2)	-28.7 (1.9)	-12.6 (-18.2, -7.9)
	Placebo	95.8 (10.8)	-16.0 (2.1)	--
4	LATUDA (40 mg/day)	96.5 (11.5)	-19.2 (1.7)	-2.1 (-7.0, 2.8)
	LATUDA (80 mg/day)*	96.0 (10.8)	-23.4 (1.8)	-6.4 (-11.3, -1.5)
	LATUDA (120 mg/day)	96.0 (9.7)	-20.5 (1.8)	-3.5 (-8.4, 1.4)
	Placebo	96.8 (11.1)	-17.0 (1.8)	--
5	LATUDA (80 mg/day)*	97.7 (9.7)	-22.2 (1.8)	-11.9 (-16.9, -6.9)
	LATUDA (160 mg/day)*	97.5 (11.8)	-26.5 (1.8)	-16.2 (-21.2, -11.2)
	Quetiapine Extended-release (600 mg/day)*[b]	97.7 (10.2)	-27.8 (1.8)	-17.5 (-22.5, -12.4)

Placebo	96.6 (10.2)	-10.3 (1.8)	--

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

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Included for assay sensitivity.

* Doses statistically significantly superior to placebo.

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

Adolescents (13-17 years)

The efficacy of LATUDA, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adolescents (13 to 17 years) who met DSM-IV-TR criteria for schizophrenia (N=326). Patients were randomized to one of two fixed-doses of LATUDA (40 or 80 mg/day) or placebo.

The primary rating instrument used to assess psychiatric signs and symptoms was the PANSS. The key secondary instrument was the CGI-S.

For both dose groups, LATUDA was superior to placebo in reduction of PANSS and CGI-S scores at Week 6. On average, the 80 mg/day dose did not provide additional benefit compared to the 40 mg/day dose.

The primary efficacy results are provided in Table 36.

Table 36: Primary Efficacy Results (PANSS Total Score) for the Adolescent Schizophrenia Study

Treatment Group	Primary Efficacy Measure: PANSS		
	Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference (95% CI)**
LATUDA (40 mg/day)*	94.5 (10.97)	-18.6 (1.59)	-8.0 (-12.4, -3.7)
LATUDA (80 mg/day)*	94.0 (11.12)	-18.3 (1.60)	-7.7 (-12.1, -3.4)
Placebo	92.8 (11.08)	-10.5 (1.59)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.2. Depressive Episodes Associated with Bipolar I Disorder

Adults

Monotherapy

The efficacy of LATUDA, as monotherapy, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.5 years,

range 18 to 74) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=485). Patients were randomized to one of two flexible-dose ranges of LATUDA (20 to 60 mg/day, or 80 to 120 mg/day) or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S), a clinician-rated scale that measures the subject's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

For both dose groups, LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6. The primary efficacy results are provided in Table 37. The high dose range (80 to 120 mg per day) did not provide additional efficacy on average, compared to the low dose range (20 to 60 mg per day).

Adjunctive Therapy with Lithium or Valproate

The efficacy of LATUDA, as an adjunctive therapy with lithium or valproate, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (mean age of 41.7 years, range 18 to 72) who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=340). Patients who remained symptomatic after treatment with lithium or valproate were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo.

The primary rating instrument used to assess depressive symptoms in this study was the MADRS. The primary endpoint was the change from baseline in MADRS score at Week 6. The key secondary instrument was the CGI-BP-S scale.

LATUDA was superior to placebo in reduction of MADRS and CGI-BP-S scores at Week 6, as an adjunctive therapy with lithium or valproate (Table 37).

Table 37: Primary Efficacy Results for Adult Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

Study	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Monotherapy study	LATUDA (20-60 mg/day)*	30.3 (5.0)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	LATUDA (80-120 mg/day)*	30.6 (4.9)	-15.4 (0.8)	-4.6 (-6.9, -2.3)
	Placebo	30.5 (5.0)	-10.7 (0.8)	--

Adjunctive Therapy study	LATUDA (20-120 mg/day)* + lithium or valproate	30.6 (5.3)	-17.1 (0.9)	-3.6 (-6.0, -1.1)
	Placebo + lithium or valproate	30.8 (4.8)	-13.5 (0.9)	--

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

[a] Difference (drug minus placebo) in least-squares mean change from baseline. * Treatment group statistically significantly superior to placebo.

Pediatric Patients (10 to 17 years)

The efficacy of LATUDA was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of pediatric patients (10 to 17 years) who met DSM-5 criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=343). Patients were randomized to flexibly dosed LATUDA 20 to 80 mg/day or placebo. At the end of the clinical study, most patients (67%) received 20 mg/day or 40 mg/day.

The primary rating scale used to assess depressive symptoms in this study was the Children's Depression Rating Scale, Revised (CDRS-R) total score. The CDRS-R is a 17-item clinician-rated scale with total scores ranging from 17 to 113. The primary endpoint was the change from baseline in CDRS-R score at Week 6. The key secondary endpoint was the change from baseline in CGI-BP-S depression score.

LATUDA was superior to placebo in reduction of CDRS-R total score and CGI-BP-S depression score at Week 6. The primary efficacy results are provided in Table 38.

Table 38 Primary Efficacy Results for the Study in Depressive Episodes Associated with Bipolar I Disorder (CDRS-R Total Score) in Pediatric Patients (10 to 17 years)

Treatment Group	Primary Efficacy Measure: CDRS-R		
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
LATUDA (20 to 80 mg/day)*	59.2 (8.24)	-21.0 (1.06)	-5.7 (-8.4,-3.0)
Placebo	58.6 (8.26)	-15.3 (1.08)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, unadjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Treatment group statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (20 mg or 40 mg), white to off-white, oblong (60 mg), pale green, oval (80 mg) or white to off-white, oval (120 mg) and identified with strength-specific one-sided debossing, “L20” (20 mg), “L40” (40 mg), “L80” (80 mg) or “L120” (120 mg). Tablets are supplied in the following strengths and package configurations (Table 39).

Table 39: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration	NDC Code
20 mg	Bottles of 30	63402-302-30
	Bottles of 90	63402-302-90
	Bottles of 500	63402-302-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-302-10 Carton 63402-302-01 Blister
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
60 mg	Bottles of 30	63402-306-30
	Bottles of 90	63402-306-90
	Bottles of 500	63402-306-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-306-10 Carton 63402-306-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister
120 mg	Bottles of 30	63402-312-30
	Bottles of 90	63402-312-90
	Bottles of 500	63402-312-50

Tablet Strength	Package Configuration	NDC Code
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-312-10 Carton 63402-312-01 Blister

Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) *[See USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behavior

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning, Warning and Precautions (5.2)]*.

Neuroleptic Malignant Syndrome

Counsel patients about a potentially fatal adverse reaction referred to as Neuroleptic Malignant Syndrome (NMS). Advise patients, family members, or caregivers to contact healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of LATUDA. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males *[see Warnings and Precautions (5.7)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking LATUDA *[see Warnings and Precautions (5.8)]*.

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.9)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

Activation of Mania or Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.14)*].

Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, because there is a potential for drug interactions *[see Drug Interactions (7)]*.

Pregnancy

Advise patients that LATUDA may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy *[see Use in Specific Populations (8.1)]*.



Manufactured for:
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Marlborough, MA 01752 USA

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

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MEDICATION GUIDE
LATUDA (luh-TOO-duh)
(lurasidone hydrochloride)
tablets

What is the most important information I should know about LATUDA?

LATUDA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** Medicines like LATUDA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). LATUDA is not approved for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts or actions in children and young adults.** Antidepressant medicines may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed.
  - o **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or a history of suicidal thoughts or actions.

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- o Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- o Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- o Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse depression
- feeling very agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity and talking (mania)
- attempts to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

What is LATUDA?

LATUDA is a prescription medicine used:

- To treat people 13 years of age or older with schizophrenia.
- Alone to treat people 10 years of age and older with depressive episodes that happen with Bipolar I Disorder (bipolar depression).
- With the medicine lithium or valproate to treat adults with depressive episodes that happen with Bipolar I Disorder (bipolar depression).

It is not known if LATUDA is safe and effective in children:

- less than13 years of age with schizophrenia
- less than 10 years of age with bipolar depression
- for the treatment of irritability associated with autistic disorder

Do not take LATUDA if you are:

- allergic to lurasidone hydrochloride or any of the ingredients in LATUDA. See the end of this Medication Guide for a complete list of ingredients in LATUDA.
- taking certain other medicines called CYP3A4 inhibitors or inducers including ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, rifampin, avasimibe, St. John's wort, phenytoin, or carbamazepine. Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before taking LATUDA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or stroke

- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or have a family history of diabetes or high blood sugar.
- have or have had high levels of total cholesterol or triglycerides
- have or have had high prolactin levels
- have or have had low white blood cell count
- have or have had seizures
- have or have had kidney or liver problems
- are pregnant or plan to become pregnant. It is not known if LATUDA will harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take LATUDA during pregnancy.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with LATUDA.
  - If you become pregnant during treatment with LATUDA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. It is not known if LATUDA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LATUDA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

LATUDA and other medicines may affect each other causing possible serious side effects. LATUDA may affect the way other medicines work, and other medicines may affect how LATUDA works.

Your healthcare provider can tell you if it is safe to take LATUDA with your other medicines. Do not start or stop any other medicines during treatment with LATUDA without talking to your healthcare provider first.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take LATUDA?

- Take LATUDA exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking LATUDA without first talking to your healthcare provider.
- Take LATUDA by mouth, with food (at least 350 calories).
- If you take too much LATUDA, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

What should I avoid while taking LATUDA?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how LATUDA affects you. LATUDA may make you drowsy.
- Avoid eating grapefruit or drinking grapefruit juice during treatment with LATUDA. Grapefruit and grapefruit juice may affect the amount of LATUDA in your blood.
- Do not become too hot or dehydrated during treatment with LATUDA.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of LATUDA?

LATUDA may cause serious side effects, including:

- **See "What is the most important information I should know about LATUDA?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - confusion
  - changes in your breathing, heart rate, and blood pressure
  - stiff muscles
  - increased sweating
- **Uncontrolled body movements (tardive dyskinesia).** LATUDA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking LATUDA.

Tardive dyskinesia may also start after you stop taking LATUDA.

- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take LATUDA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start and during treatment with LATUDA.

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with LATUDA:

    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.**
  - **weight gain.** You and your healthcare provider should check your weight regularly during treatment with LATUDA.
- **Increased prolactin levels in your blood (hyperprolactinemia).** Your healthcare provider may do blood tests to check your prolactin levels during treatment with LATUDA. Tell your healthcare provider if you have any of the following signs and symptoms of hyperprolactinemia:

  Females:
  - absence of your menstrual cycle
  - secretion of breast milk when you are not breastfeeding

  Males:
  - problems getting or maintaining an erection (erectile dysfunction)
  - enlargement of breasts (gynecomastia)
- **Low white blood cell count.** Your healthcare provider may do blood tests during the first few months of treatment with LATUDA.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** LATUDA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions)**
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking LATUDA?"
- **Mania or hypomania** (manic episodes) in people with a history of bipolar disorder. Symptoms may include:
  - greatly increased energy
  - racing thoughts
  - unusually grand ideas
  - talking more or faster than usual
  - severe problems sleeping
  - reckless behavior
  - excessive happiness or irritability
- **Difficulty swallowing**

The most common side effects of LATUDA include:

- **Adults with schizophrenia:**
  - sleepiness or drowsiness
  - restlessness and feeling like you need to move around (akathisia)
  - difficulty moving, slow movements, muscle stiffness, or tremor
  - nausea
- **Children 13 to 17 years of age with schizophrenia:**
  - sleepiness or drowsiness
  - nausea
  - restlessness and feeling like you need to move around (akathisia)
  - difficulty moving, slow movements, muscle stiffness, or tremor
  - runny nose
  - vomiting
- **Adults with bipolar depression:**
  - restlessness and feeling like you need to move around (akathisia)

- difficulty moving, slow movements, muscle stiffness, or tremor
- sleepiness or drowsiness

- **Children 10 to 17 years of age with bipolar depression:**
  - Nausea
  - weight gain
  - problems sleeping (insomnia)

These are not all of the possible side effects of LATUDA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LATUDA?

- Store LATUDA tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LATUDA and all medicines out of the reach of children.

General information about the safe and effective use of LATUDA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LATUDA for a condition for which it was not prescribed. Do not give LATUDA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LATUDA that is written for health professionals.

What are the ingredients in LATUDA?

Active ingredient: lurasidone hydrochloride

Inactive ingredients: mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake

Manufactured for: Sunovion Pharmaceuticals Inc. Marlborough, MA 01752 USA

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For more information, go to www.LATUDA.com or call 1-888-394-7377.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 3/2018

添付文書ハイライト
この概要には、LATUDA を安全かつ効果的に使用するために必要な情報がすべて含まれているわけではない。LATUDA の詳細処方情報を参照すること。

LATUDA（ルラシドン塩酸塩）錠（経口剤）

米国での最初の承認：2010 年

警告：認知症関連の精神病を有する高齢者における死亡率の増加、自殺念慮及び自殺行為
枠組み警告の詳細については、詳細処方情報を参照すること。

- **抗精神病薬による治療を受けている認知症関連の精神病を有する高齢患者では、死亡のリスクが増加する。LATUDA は、認知症に関わる精神病を有する患者への投与は認められていない（5.1）。**
- **抗うつ剤は、小児患者および若年成人患者における自殺念慮および自殺行為のリスクを増加させた。自殺念慮および自殺行為の臨床的悪化および発生を注意深くモニタリングすること（5.2）。**

----------最近の主な変更点----------

枠組み警告	2018/3
効能・効果（1）	2018/3
用法・用量（2.2）	2018/3
警告および使用上の注意	2018/3

(5.1, 5.2, 5.4, 5.5, 5.6, 5.7, 5.9, 5.12, 5.11, 5.14)

----------効能・効果----------

LATUDA は、以下の治療を適応とする非定型抗精神病薬である。

- 成人および青年（13～17 歳）の統合失調症（1、14.1）
- 成人および小児（10～17 歳）における双極 I 型障害（双極性障害のうつ症状）に伴う大うつ病エピソードに対する単剤療法（1、14.2）
- 成人における双極 I 型障害（双極性障害のうつ症状）に伴う大うつ病エピソードに対するリチウムまたはバルプロ酸との併用療法（1、14.2）

----------用法・用量----------

LATUDA は食事（350 kcal 以上）とともに服用する。LATUDA を食事とともに服用すると、同剤の吸収が大幅に増加する（2.3、12.3）。

適応症	開始用量	推奨用量
統合失調症－成人（2.1）	1 日当たり 40 mg	1 日当たり 40 mg ～160 mg
統合失調症－青年（13～17 歳）（2.1）	1 日当たり 40 mg	1 日当たり 40 mg ～80 mg
双極性障害のうつ症状－成人（2.2）	1 日当たり 20 mg	1 日当たり 20 mg ～120 mg
双極性障害のうつ症状－小児（10～17 歳）（2.2）	1 日当たり 20 mg	1 日当たり 20 mg ～80 mg

- 中等度および重度の腎機能障害：推奨開始用量は 1 日当たり 20 mg、最大用量は 1 日当たり 80 mg が推奨される（2.4、8.6）。
- 中等度および重度の肝機能障害：推奨開始用量は 1 日当たり 20 mg である。最大用量は中等度の肝機能障害の場合は 1 日当たり 80 mg、重度の肝機能障害の場合は 1 日当たり 40 mg が推奨される（2.5、8.7）。
- 中等度の CYP3A4 阻害剤（ジルチアゼムなど）の併用：LATUDA の用量は、元の用量の半分に減量する必要がある。推奨開始用量は 1 日当たり 20 mg である。最大推奨用量は 1 日当たり 80 mg である（2.6、7.1）。
- 中等度の CYP3A4 誘導剤の併用：LATUDA の増量が必要な場合がある（2.6、7.1）。

----------剤型・含量----------

錠剤： 20 mg、40 mg、60 mg、80 mg、120 mg（3）

----------禁忌----------

- LATUDA または製剤に含まれる成分に対して過敏症の既往歴のある者（4）。
- 強力な CYP3A4 阻害剤（ケトコナゾールなど）の併用（2.6、4、7.1）。
- 強力な CYP3A4 誘導剤（リファンピシンなど）の併用（2.6、4、7.1）。

----------警告および使用上の注意----------

- 認知症関連の精神病を有する高齢患者における脳血管系の副作用：脳血管系の有害事象（脳卒中、一過性脳虚血発作など）の発現率増加（5.3）。
- 悪性症候群：投薬の即時中止と慎重なモニタリングによって管理すること（5.4）。
- 遅発性ジスキネジア：臨床的に妥当な場合は投薬を中止すること（5.5）。
- 代謝変化：高血糖および糖尿病、脂質異常症、体重増加についてモニタリングすること（5.6）。
- 高プロラクチン血症：プロラクチン増加が起こることがある（5.7）。
- 白血球減少症、好中球減少症、顆粒球減少症：既存の白血球数（WBC）低値、もしくは白血球減少症または好中球減少症の既往歴のある患者の全血球算定（CBC）を実施すること。他の原因要素がない場合に、臨床的に重大な WBC の低下が見られた時は、LATUDA の中止を検討すること（5.8）。
- 起立性低血圧および失神：心拍数および血圧をモニタリングし、心血管疾患または脳血管疾患の既往歴のある患者には注意を促し、脱水または失神のリスクを警告すること（5.9）。

----------副作用----------

一般的に見られる副作用（発現率が 5%以上で、プラセボに比べ発現率が 2 倍以上）（6.1）：

- 統合失調症の成人患者：傾眠、アカシジア、錐体外路症状、悪心
- 統合失調症の青年患者（13～17 歳）：傾眠、悪心、アカシジア、錐体外路症状（アカシジア以外）、鼻炎（80 mg のみ）、嘔吐
- 双極性障害のうつ症状の成人患者：アカシジア、錐体外路症状、傾眠
- 双極性障害のうつ症状の小児患者（10～17 歳）：悪心、体重増加、不眠症

副作用が疑われる事例の報告は、Sunovion Pharmaceuticals Inc.（1-877-737-7226）または FDA（1-800-FDA-1088 または www.fda.gov/medwatch）に連絡すること。

----------特殊な集団における使用----------

- 妊婦：妊娠後期に曝露を受けた新生児に錐体外路症状および／または離脱症状が起きる可能性がある（8.1）。

17 患者カウンセリング情報および薬剤ガイドを参照すること。

改訂：2018 年 3 月

参照 ID：4228037

詳細処方情報： 目次*
警告：
認知症関連の精神病を有する高齢者における死亡率の増加、自殺念慮及び自殺行為

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*本添付文書から削除されたセクションまたはサブサブセクションは掲載していない。

参照 ID：4228037

添付文書

警告：認知症関連の精神病を有する高齢者における死亡率の増加、自殺念慮及び自殺行為

認知症関連の精神病を有する高齢患者の死亡率の増加
抗精神病薬による治療を受けている認知症関連の精神病を有する高齢患者では、死亡のリスクが増加する。LATUDA は、認知症に関わる精神病を有する患者への投与は認められていない*［警告および使用上の注意（5.1）を参照］*。

自殺念慮および自殺行為
抗うつ剤は、短期試験において小児および若年成人における自殺念慮および自殺行為のリスクを増加させた。抗うつ剤治療を受けているすべての患者に対し、自殺念慮および自殺行為の臨床的悪化と発生を注意深くモニタリングすること*［警告および使用上の注意（5.2）を参照］*。

1　効能・効果

LATUDA は以下を適応とする：

•統合失調症の成人患者および青年患者（13～17 歳）の治療*［臨床試験（14.1）を参照］*。

•双極 I 型障害（双極性障害のうつ症状）に伴う大うつ病エピソードを有する成人患者および小児患者（10～17 歳）に対する単剤療法*［臨床試験（14.2）を参照］*。

•双極 I 型障害（双極性障害のうつ症状）の大うつ病エピソードを有する成人患者に対するリチウムまたはバルプロ酸との併用療法*［臨床試験（14.2）を参照］*。

2　用法・用量

2.1　統合失調症

成人

LATUDA の推奨開始用量は 1 日 1 回 40 mg である。初期用量の漸増は不要である。LATUDA は、1 日当たり 40 mg～160 mg の用量範囲で有効であることが示されている*［臨床試験（14.1）を参照］*。最大推奨用量は 1 日当たり 160 mg である。

青年（13～17 歳）

LATUDA の推奨開始用量は 1 日 1 回 40 mg である。初期用量の漸増は不要である。LATUDA は、1 日当たり 40 mg～80 mg の用量範囲で有効であることが示されている*［臨床試験（14.1）を参照］*。最大推奨用量は 1 日当たり 80 mg である。

参照 ID：4228037

2.2 双極 I 型障害に伴う大うつ病エピソード

成人

単剤療法またはリチウムまたはバルプロ酸での併用療法を受けている場合、LATUDA の推奨開始用量は 1 日 1 回 20 mg である。初期用量の漸増は不要である。LATUDA は 1 日当たり 20 mg～120 mg の用量範囲で単剤及びリチウムまたはバルプロ酸との併用療法の有効性が示されている*［臨床試験（14.2）を参照］*。単剤療法または併用療法を受けている場合、推奨最大用量は 1 日当たり 120 mg である。単剤療法試験において、高い用量範囲（1 日当たり 80 mg～120 mg）は、低い用量範囲（1 日当たり 20 mg～60 mg）と比べ、全般的に付加的な有効性を示さなかった*［臨床試験（14.2）を参照］*。

小児患者（10～17 歳）

単剤療法での LATUDA の推奨開始用量は 1 日 1 回 20 mg である。初期用量の漸増は不要である。臨床反応に基づき、1 週間後に増量することは可能である。LATUDA は、単剤療法として 1 日当たり 20 mg～80 mg の用量範囲で有効であることが示されている。臨床試験の終了時点で、被験者の大多数（67%）は 1 日 1 回 20 mg または 40 mg の投与を受けていた*［臨床試験（14.2）を参照］*。最大推奨用量は 1 日当たり 80 mg である。

双極性障害に伴う躁病の治療における LATUDA の有効性は確立されていない。

2.3 投与方法

LATUDA は食事（350 kcal 以上）とともに服用する。LATUDA を食事とともに服用すると、同剤の吸収が大幅に高められる。食事との同時投与は、AUC を約 2 倍、C_{max} を約 3 倍に増加させる。臨床試験では、LATUDA は食事とともに投与されている*［薬効薬理（12.3）を参照］*。

長期使用（すなわち 6 週間を超える使用）に関する LATUDA の効果は、対照試験では確立されていない。したがって、LATUDA を長期にわたって使用することを選択する医師は、個々の患者について、本薬剤の長期的な有用性を定期的に再評価すること*［用法・用量（2.1 および 2.2）を参照］*。

2.4 腎機能障害患者における用量調節

中等度（クレアチニンクリアランス：30～<50 mL/分）および重度（クレアチニンクリアランス<30 mL/分）の腎機能障害患者においては、用量調節が推奨される。推奨開始用量は 1 日当たり 20 mg である。このような患者の用量は、1 日当たり 80 mg を超えないこと*［特殊な集団における使用（8.6）を参照］*。

2.5 肝機能障害患者における用量調節

中等度（Child-Pugh スコア = 7～9）および重度（Child-Pugh スコア = 10～15）の肝機能障害患者においては、用量調節が推奨される。推奨開始用量は 1 日当たり 20 mg である。中等度の肝機能障害を有する患者の場合は 1 日当たり 80 mg、重度の肝機能障害を有する患者の場合は 1 日当たり 40 mg の用量を超えないこと*［特殊な集団における使用（8.7）を参照］*。

参照 ID：4228037

2.6 CYP3A4 阻害剤および CYP3A4 誘導剤との薬物相互作用による用量調節

CYP3A4 阻害剤との併用投与

LATUDA は、強力な CYP3A4 阻害剤（ケトコナゾール、クラリスロマイシン、リトナビル、ボリコナゾール、ミベフラジルなど）と併用しないこと*［禁忌（4）を参照］*。

LATUDA が処方されており、中等度の CYP3A4 阻害剤（ジルチアゼム、アタザナビル、エリスロマイシン、フルコナゾール、ベラパミルなど）が治療に追加された場合、LATUDA の用量は元の用量の半分に減らす必要がある。同様に、中等度の CYP3A4 阻害剤が処方されており、LATUDA が治療に追加された場合、LATUDA の推奨開始用量は 1 日当たり 20 mg で、推奨最大用量は 1 日当たり 80 mg である*［禁忌（4）、薬物相互作用（7.1）を参照］*。

グレープフルーツ及びグレープフルーツジュースは CYP3A4 を阻害し、LATUDA 濃度を変化させることがあるため、LATUDA を服用している患者はこれらを避けること*［薬物相互作用（7.1）を参照］*。

CYP3A4 誘導剤との併用投与

LATUDA は、強力な CYP3A4 誘導剤（リファンピシン、アバシミブ、セイヨウオトギリソウ、フェニトイン、カルバマゼピンなど）と併用すべきではない*［禁忌（4）、薬物相互作用（7.1）を参照］*。LATUDA を中等度の CYP3A4 誘導剤の長期治療（7 日以上）の後に併用する場合は、LATUDA の増量が必要な場合がある。

3 剤型・含量

LATUDA 錠は次の形状と色の製剤が市販されており（表 1）、それぞれ片面に以下のような刻印がある：

表 1 LATUDA 錠の外観

錠剤の含量	錠剤の色／形	錠剤の刻印
20 mg	白色～帯黄白色、円形	L20
40 mg	白色～帯黄白色、円形	L40
60 mg	白色～帯黄白色、長楕円形	L60
80 mg	薄緑色、楕円形	L80
120 mg	白色～帯黄白色、楕円形	L120

4 禁忌

- ルラシドン塩酸塩または製剤に含まれる何らかの成分に対する過敏症の既往歴のある患者。ルラシドンでは血管浮腫が観察されている*［副作用（6.1）を参照］*。

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- 強力な CYP3A4 阻害剤（ケトコナゾール、クラリスロマイシン、リトナビル、ボリコナゾール、ミベフラジルなど）*[薬物相互作用（7.1）を参照]*。
- 強力な CYP3A4 誘導剤（リファンピシン、アバシミブ、セイヨウオトギリソウ、フェニトイン、カルバマゼピンなど）*[薬物相互作用（7.1）を参照]*。

5 警告および使用上の注意

5.1 認知症関連の精神病を有する高齢患者の死亡率の増加

抗精神病薬による治療を受けている認知症関連の精神病を有する高齢患者では、死亡のリスクが増加する。主として非定型抗精神病薬を投与している患者に対する 17 件のプラセボ対照比較試験（試験期間の最頻値は 10 週間）の解析から、薬剤を投与された患者の死亡リスクが、プラセボを投与された患者と比べて 1.6～1.7 倍高いことが示された。10 週間の標準的対照比較試験で、薬剤投与群の死亡率は約 4.5%であり、プラセボ群では約 2.6%であった。死因はさまざまであったが、その多くは心血管（心不全、突然死など）または感染症（肺炎など）であることが示された。LATUDA は、認知症に関わる精神病を有する患者への投与は認められていない *[枠組み警告、ならびに警告および使用上の注意（5.3）を参照]*。

5.2 小児および若年成人患者における自殺念慮および自殺行為

約 77,000 例の成人患者および 4,400 例を超える小児患者を含む、抗うつ剤（SSRI および他のクラスの抗うつ剤）のプラセボ対照比較試験の併合解析では，小児患者および若年成人患者における自殺念慮および自殺行為の発現率がプラセボ投与患者よりも抗うつ剤投与患者で高かった。治療患者 1,000 例当たりの自殺念慮および自殺行為の症例数のプラセボとの差異を表 2 に示す。

小児患者を対象とした試験では、自殺は発生していない。成人患者を対象とした試験では自殺が発生しているが、その数は抗うつ剤の自殺への作用に関するいかなる結論を下すにも不十分であった。

表 2 小児患者および成人患者を対象とした抗うつ剤のプラセボ対照比較試験の併合解析における自殺念慮または自殺行為のリスクの差異（症例数比較）

年齢層	治療患者 1000 人当たりの自殺念慮および自殺行為の症例数のプラセボとの差異
	プラセボと比較した増加
<18	14 例の増加
18-24	5 例の増加
	プラセボと比較した減少
25-64	1 例の減少
≥65	6 例の減少

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小児患者および若年成人患者における自殺念慮および自殺行為のリスクが、4 ヵ月を超える長期使用にまで及ぶかどうかは不明である。しかし、大うつ病性障害を有する成人のプラセボ対照維持試験から、抗うつ剤がうつ病の再発を遅延することができるという実質的証拠がある。

抗うつ剤治療を受けているすべての患者は、臨床的な悪化や自殺念慮および自殺行為の発生に対し、特に薬剤治療の最初の数ヵ月間および用量変更時において、モニタリングが必要である。患者の家族または介護者に、行動変化のモニタリングを行い、医療提供者に報告するよう指導すること。うつ病が持続的に悪化している患者、または、自殺念慮または自殺行為の発生を経験している患者においては、LATUDA の中止の可能性を含む治療レジメンの変更を検討する必要がある。

5.3 認知症関連の精神病を有する高齢患者の脳卒中を含む脳血管系副作用

認知症の高齢患者を対象としたリスペリドン、アリピプラゾールおよびオランザピンに関するプラセボ対照試験では、死亡を含む脳血管系副作用（脳血管発作、一過性脳虚血発作）の発現率が、薬剤投与患者でプラセボ投与患者よりも高かった。LATUDA は、認知症に関わる精神病を有する患者への投与は認められていない *[枠組み警告、ならびに警告および使用上の注意（5.1）を参照]*。

5.4 悪性症候群

時として悪性症候群（NMS）と呼ばれる、死に至る可能性がある症状が、LATUDA を含む抗精神病薬の投与に関連して報告されている。NMS の臨床症状は高熱、筋固縮、精神状態の変化および自律神経不安定症である。さらに、クレアチンホスホキナーゼ増加、ミオグロビン尿（横紋筋融解症）および急性腎不全なども含まれる場合がある。

NMS が疑われる場合は、直ちに LATUDA を中止し、集中的な対症療法およびモニタリングを行うこと。

5.5 遅発性ジスキネジア

遅発性ジスキネジアは、不可逆的で不随意性の運動障害からなる症候群で、抗精神病薬治療を受けた患者に発現する可能性がある。本症候群の有病率は、高齢者（特に高齢女性）において最も高くなっているが、抗精神病薬の投与を開始する時点で、どの患者が症候群を発現しやすいかを予測する際に、推定有病率に頼ることは不可能である。遅発性ジスキネジアを引き起こす可能性に関して、抗精神病薬間で差異があるかどうかは分かっていない。

遅発性ジスキネジアを発現するリスク、およびそれが不可逆になる可能性は、治療期間、および患者に投与する抗精神病薬の総累積用量が増えるにつれ増加すると考えられている。しかし、発現率ははるかに低いが、低用量で比較的短期間の投与下でも、同症候群が発現する可能性があり、投与中止後であっても発現する場合がある。

抗精神病薬の投与を中止した場合には、部分的にあるいは完全に寛解する場合がある。しかし、抗精神病薬の投与それ自体は、同症候群の徴候および症状を抑制（あるいは、部分的に抑制）する可能性があり、それ故に、基礎疾患の臨床経過を隠す場合がある。症状抑制が、症候群の長期的な経過に及ぼす影響は知られていない。

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これらを考慮に入れて、LATUDA は遅発性ジスキネジアの発現を最小限に抑える可能性が最も高い方法で処方すべきである。長期間の抗精神病薬投与は一般に、(1) 抗精神病薬に反応することが知られている疾患を持つ患者、(2) 有効性が同じだが潜在的にそれほど有害でない代替治療を利用できないまたはそれらに不適応である患者への治療手段として行われる。長期間の治療が必要な患者では、満足な臨床反応を生みだす最低用量および最短期間を模索するべきである。継続的な治療の必要性を定期的に再検討すること。

LATUDA を投与されている患者に遅発性ジスキネジアの徴候と症状が現われた場合は、投与中止を考慮すること。しかし、一部の患者では、同症候群を来しても LATUDA による治療が必要となる場合がある。

5.6 代謝変化

非定型抗精神病薬は、心血管系／脳血管系のリスクを増加させうる代謝変化を伴う。この代謝変化には、高血糖、脂質異常症、および体重増加が含まれる。この種の薬剤はすべて、ある程度の代謝変化を生じることが示されているが、それぞれの薬剤について固有のリスクプロファイルがある。

高血糖および糖尿病

非定型抗精神病薬による治療を受けた患者で高血糖が報告されており、症例によっては極度でケトアシドーシスまたは高浸透圧性昏睡あるいは死亡に関連した症例も報告されている。非定型抗精神病薬の使用と血糖値異常の関係の評価は、統合失調症の患者に糖尿病の背景リスクが増加する可能性および一般母集団の糖尿病発現率の増加により複雑化する。これらの交絡因子をかんがみて、非定型抗精神病薬の使用と高血糖関連の有害事象との関係は、完全には解明されていない。しかしながら、疫学的研究では、非定型抗精神病薬による治療を受けた患者における、高血糖関連の有害事象のリスクの増加が示唆されている。

非定型抗精神病薬による治療を開始した糖尿病と確定診断されている患者では、血糖コントロールの悪化に備えて定期的にモニタリングする必要がある。非定型抗精神病薬による治療を開始する糖尿病危険因子を有する患者（肥満、糖尿病の家族歴など）は、治療開始時および治療中、定期的に空腹時血糖検査を受けるべきである。非定型抗精神病薬による治療を受けたすべての患者で、多飲症、多尿、過食、および脱力を含む高血糖症の症状がないかどうかモニタリングすべきである。非定型抗精神病薬による治療中に高血糖の症状を示す患者には、空腹時血糖検査を行うべきである。一部の例では、非定型抗精神病薬を中止すると高血糖が消失した。しかしながら一部の患者は、被疑薬を中止したにもかかわらず糖尿病に対する治療を継続する必要があった。

統合失調症

成人

複数の短期プラセボ対照統合失調症試験を統合したデータを表 3 に示す。

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表 3　　成人を対象とする統合失調症試験における空腹時血糖値の変化

		LATUDA			
	プラセボ	**20 mg/日**	**40 mg/日**	**80 mg/日**	**120 mg/日**	**160 mg/日**
ベースラインからの平均値の変化（mg/dL）						
	n=680	**n=71**	**n=478**	**n=508**	**n=283**	**n=113**
血清グルコース	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
126 mg/dL 超にシフトした患者の割合						
血清グルコース（126 mg/dL 以上）	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/260)	5.6% (6/108)

非対照の統合失調症に対する長期投与試験（主に非盲検継続試験）においては、LATUDA に関連するグルコース平均変化は、24 週で+1.8 mg/dL（n=355）、36 週で+0.8 mg/dL（n=299）、52 週で+2.3 mg/dL（n=307）であった。

青年

青年および成人の統合失調症を対象とする試験でも空腹時血糖値の変化は同様であった。青年を対象とする短期プラセボ対照比較試験では、空腹時血清グルコースの平均変化は、プラセボ群で-1.3 mg/dL（n=95）、40 mg/日群で+0.1 mg/dL（n=90）、80 mg/群で+1.8 mg/dL（n=92）であった。

双極性障害のうつ症状

成人

単剤療法

成人の双極性障害うつを対象とした短期可変用量プラセボ対照単剤療法試験のデータを表 4 に示す。

表 4　　成人の双極性障害うつを対象とした短期可変用量プラセボ対照単剤療法試験における空腹時血糖値の変化

		LATUDA	
	プラセボ	**20～60 mg/日**	**80～120 mg/日**
ベースラインからの平均値の変化（mg/dL）			
	n=148	**n=140**	**n=143**
血清グルコース	+1.8	-0.8	+1.8
126 mg/dL 超にシフトした患者の割合			
血清グルコース（126 mg/dL 以上）	4.3% (6/141)	2.2% (3/138)	6.4% (9/141)

患者は、20～60 mg/日の可変用量 LATUDA、80～120 mg/日の LATUDA、またはプラセボに無作為化されている。

双極性障害のうつ症状を対象とした短期試験の単剤療法として LATUDA を投与され、非対照非盲検長期試験でも継続投与された患者のグルコースの平均変化量は、24 週で+1.2 mg/dL（n=129）であった。

参照 ID：4228037