第１７回　未承認薬使用問題検討会議　議事次第

平成 20 年 6 月 30 日(月)14:00～16:00
はあといん乃木坂　フルール

議　　事

１．検討する必要のある未承認薬について

２．その他

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資料　１　　「未承認薬使用問題検討会議」における検討終了から６ヶ月以上経過後、治験が開始されていない品目について（照会の回答）

資料　２　　平成 20 年 3 月～5 月に提出された早期承認に係る要望書一覧

資料　３　　平成 20 年 3 月～5 月に欧米４カ国のいずれかの国で新たに承認された医薬品（類型Ｉ）

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参考資料　１　「未承認薬使用問題検討会議」開催要綱

参考資料　２　「未承認薬使用問題検討会議」構成員

参考資料　３　「未承認薬使用問題検討会議」における対象医薬品

参考資料　４　未承認薬を治験対象とする場合の考え方

参考資料　５　ワーキンググループの設置について

参考資料　６　未承認薬使用問題検討会議での検討状況

資料 1

「未承認薬使用問題検討会議」における検討終了から6ヶ月以上経過後、治験が開始されていない品目について（照会の回答）

（平成20年6月30日現在）

No.	検討会議開催日	成分名	対象疾病	検討会議での主な検討結果	今回の回答	企業名
11	第5回（平成17年7月）	ストレプトゾシン	膵島細胞癌	早期に治験が開始されるべき	ライセンス交渉中	（調整中）
16	第6回（平成17年10月）	クロファラビン	小児急性リンパ性白血病	早期に治験が開始されるべき	治験準備中（治験計画を機構、関係学会と相談しつつ作成中）	ジェンザイム・ジャパン
18	第7回（平成18年1月）	ペグアスパラガーゼ	L-アスパラギナーゼに過敏症の急性リンパ性白血病	早期に治験が開始されるべき	導入先と協議中。厚生労働省からも、導入先に早期開発への協力を依頼	（調整中）
19	第7回（平成18年1月）	フェニル酪酸ナトリウム	尿素サイクル異常症	欧米臨床データ及び国内使用症例データ等を基に早期に承認申請が行われるべき。審査期間中に国内治験データ等が収集されるべき	米国企業と導入に向け交渉中	ノーベルファーマ
20	第7回（平成18年1月）	オクスカルバゼピン	てんかん部分発作	早期に治験が開始されるべき	国内開発に着手（開発計画を検討中）	ノバルティス ファーマ
24	第8回（平成18年4月）	コニバプタン	低ナトリウム血症	我が国における有効性、安全性を注意深く検討しつつ開発を進めるべき	国内開発を断念（別添1）	アステラス製薬
25	第8回（平成18年4月）	ニチシノン	遺伝性高チロシン血症Ⅰ型	欧米臨床データをもって承認申請を認め、長期の製造販売後調査等で国内情報を収集すべき	国内開発を断念（別添2）	スウェーデン オーファン
29	第9回（平成18年7月）	フォスフェニトイン	てんかん様重積症他	早期に治験が開始されるべき	治験準備中（今秋、開始予定）	ノーベルファーマ
31	第10回（平成18年10月）	デシタビン	骨髄異形成症候群	早期に治験が開始されるべき	治験実施中（Ⅰ/Ⅱ相）	ヤンセン ファーマ
34	第11回（平成19年1月）	アレムツズマブ	B細胞性慢性リンパ性白血病	B細胞性慢性リンパ性白血病に対する治験が早期に開始されるべき	国内開発に着手（開発計画を検討中）	バイエル薬品
35	第11回（平成19年1月）	タルク	悪性胸水	早期に治験が開始されるべき	医師主導治験実施予定	ノーベルファーマ
36	第12回（平成19年4月）	ボリノスタット	皮膚T細胞性リンパ腫	皮膚T細胞性リンパ腫に対する治験が早期に開始されるべき	治験準備中（今夏、開始予定）	萬有製薬

※開発企業募集中の品目

No.	検討会議開催日	成分名	対象疾病	検討会議での主な検討結果
38	第12回（平成19年4月）	システアミン	シスチノーシス	早期に国内開発が開始されるべき
39	第12回（平成19年4月）	ベタイン	ホモシスチン尿症	早期に国内開発が開始されるべき
40	第13回（平成19年7月）	スチリペントール	乳児重症ミオクロニーてんかん	早期に治験が開始されるべき
41	第13回（平成19年7月）	経口リン酸塩製剤	原発性低リン血症性クル病	早期に国内開発が開始されるべき

（参考）　効能追加等に係る早期承認に関する要望書等

No.	薬剤名	適応疾患等	現在の効能・効果	提出者	備考
1	トリアムシノロンアセトニド	硝子体手術時の可視化	（ステロイド剤）	財団法人日本眼科学会 社団法人日本眼科医会	
2	ホスカルネット	造血幹細胞移植後のサイトメガロウィルス感染症	後天性免疫不全症候群（エイズ）患者におけるサイトメガロウィルス網膜炎	日本造血細胞移植学会	開発の意向
3	アデホビル	B型慢性肝炎（単剤使用）	ラミブジン投与中にB型肝炎ウイルスの持続的な再増殖を伴う肝機能の異常が確認された、以下の疾患におけるラミブジンとの併用によるウイルスマーカー及び肝機能の改善：B型慢性肝炎及びB型肝硬変	日本肝臓病患者団体協議会	承認申請中（2008年3月申請）
4	ゲムシタビン	卵巣がん	非小細胞肺癌、膵癌、胆道癌	卵巣がん体験者の会スマイリー他	治験開始を要請中
5	リポソーマルドキソルビシン	卵巣がん	エイズ関連カポジ肉腫	卵巣がん体験者の会スマイリー他	承認審査中（2007年1月申請）
6	γグロブリン製剤	原発性免疫不全症候群（低並びに無ガンマグロブリン血症）	適用量の拡大を要望	原発性免疫不全症候群患者と家族の会「つばさの会」 特定非営利活動法人PIDつばさの会	承認審査中（2008年3月申請）

平成２０年３月～５月に欧米４カ国のいずれかの国で新たに承認された医薬品（類型Ｉ）

１．成分名：　デスベンラファキシン（desvenlafaxine）
販売名：　pristiq
承認国：　米国（2008 年 2 月 29 日承認）
会社名：　Wyeth Pharms INC
剤形・規格：経口剤・50mg 100mg 錠、徐放薬
効能・効果：大うつ病性障害
用法・用量：50mg を 1 日 1 回投与
作用機序等：セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI）
抗うつ薬 venlafaxine の活性代謝物

○適応疾病の重篤性について：
必ずしも致死的な疾病ではない

○医療上の有用性について：
同種同効薬あり

○学会・患者団体からの要望：
なし

○国内状況：
治験実施中（Phase Ⅰ終了、Phase Ⅱ準備中）／ワイス（株）（うつ病）

２．成分名：　ベンダムスチン（bendamustine）
販売名：　米：treanda
承認国：　米国（2008 年 3 月 20 日承認）
会社名：　Cephalon
剤形・規格：注射剤・100 mg/vial
効能・効果：慢性リンパ性白血病
用法・用量：100mg/m^2 を 30 分かけて静脈内投与（day1,2）その後休薬し 28 日を 1 クールとして最大 6 クール投与する
作用機序等：アルキル化剤を活性部位とするプロドラッグ

○適応疾病の重篤性について：
致死的な疾病である

○医療上の有用性について：
同種同効薬あり

○学会・患者団体からの要望：
なし

○国内状況：
治験実施中（Phase Ⅱ）／シンバイオ製薬（株）（低悪性度 B 細胞性非ホジキンリンパ腫並びにマントル細胞リンパ腫）

3．成分名：　ダビガトラン（dabigatran）
販売名：　Pradaxa
承認国：　フランス、UK、EU 中央（2008 年 3 月 18 日承認）
会社名：　Boehringer Ingelheim International GmbH
剤形・規格：75 mg, 110 mg カプセル
効能・効果：膝や股関節の待機的全人工関節置換術（TKR）後の深部静脈血栓症（DVT）の一次予防
用法・用量：膝関節：220 mg を 1 日 1 回投与（110mg を 2 カプセル）。投与は手術終了 1-4 時間後から開始し（1 カプセル），その後 1 日 2 カプセル 1 回投与を 10 日間継続する。
股関節；膝関節：220 mg を 1 日 1 回投与（110mg を 2 カプセル）。投与は手術終了 1-4 時間後から開始し（1 カプセル），その後 1 日 2 カプセル 1 回投与を 28-35 日間継続する。
両手術ともに止血が安定しない場合、服薬開始を遅らすべきであり、手術当日に服薬を開始しない場合初回投与を 1 日 2 カプセルとする
作用機序等：直接的トロンビン阻害作用を有する

○適応疾病の重篤性について：
必ずしも致死的な疾病ではない

○医療上の有用性について：
同種同効薬あり

○学会・患者団体からの要望：
なし

○国内状況：
治験実施中（PhaseⅢ）/日本ベーリンガーインゲルハイム（株）（心房細動患者における血栓塞栓症の予防、TKR 患者における静脈血栓塞栓症の予防）

4．成分名：　レガデノソン（regadenoson）
販売名：　Lexiscan
承認国：　米国（2008 年 4 月 10 日承認）
会社名：　CV Therap
剤形・規格：0.4 mg/5mL vial; プレフィルドシリンジ
効能・効果：適正な運動負荷に耐えられない患者における心筋シンチグラム（MPI）時の心負荷（薬理学的な負荷）
用法・用量：5 mL (0.4 mg regadenoson)を急速静注し，その後直ちに生理食塩水フラッシュおよび放射性医薬品を投与する。
作用機序等：アデノシン A2A 受容体作用

○適応疾病の重篤性について：
致死的な疾病ではない（検査薬）

○医療上の有用性について：
同種・同効薬あり（アデノスキャン：第一三共）

○学会・患者団体からの要望：
なし

○国内状況：

なし

5．成分名：　PEG 化セルトリズマブ（certolizmab pegol）
販売名：　Cimzia
承認国：　米国（2008 年 4 月 22 日承認）
会社名：　UCB INC
剤形・規格：注射剤 200 mg
効能・効果：従来の治療法で奏功しない中等度～重度のクローン病の症状緩和
用法・用量：400mg を皮下投与する。投与は初回，2 週間後および 4 週間後である。反応があった場合は 400mg を 4 週間ごとに皮下投与する
作用機序等：polyethyleneglycol（PEG）によって化学的に修飾された抗腫瘍壊死因子 TNF-α ヒト化抗体

○適応疾病の重篤性について：
重篤な疾病である

○医療上の有用性について：
適応疾患に対する分子標的薬はなし

○学会・患者団体からの要望：
なし

○国内状況：
申請準備中/UCB 社・大塚製薬（株）（2009 年初めまでに申請予定）

6．成分名：　メチルトレキソン（methylnaltrexone）
販売名：　Relistor
承認国：　米国（2008 年 4 月 24 日承認）
会社名：　Progenics Pharma
剤形・規格：皮下注射剤 12 mg/0.6mL
効能・効果：下剤で十分な効果がない緩和療法を受けている疾患進行患者におけるオピオイド誘発性便秘（OIC）。
用法・用量：体重 38kg～62kg には 8mg、62kg～114kg では 12mg。それ以上の体重に対しては 0.15mg/kg で増量。1 日おきに皮下投与（24 時間以上の間隔での投与は行なわない）
作用機序等：オピオイドμ受容体阻害作用

○適応疾病の重篤性について：
致死的な疾病ではない

○医療上の有用性について：
類薬あり（緩下剤等）

○学会・患者団体からの要望：
なし

○国内状況：
なし

「未承認薬使用問題検討会議」での検討結果等について

（平成20年6月30日現在）

No.	検討会議開催日	成分名	対象疾病	検討会議での主な検討結果	検討当時の状況	現在の状況等	企業名
1	第1回（平成17年1月）	オキサリプラチン	結腸・直腸癌	承認までの間に安全性確認試験を実施すべき	承認審査中	平成17年3月18日承認、4月6日薬価収載	ヤクルト本社
2	第1回（平成17年1月）	ペメトレキセド	悪性胸膜中皮腫	早期に治験が開始されるべき	国内治験前	平成19年1月4日承認、1月19日薬価収載	日本イーライリリー
3	第1回（平成17年1月）	サリドマイド	多発性骨髄腫	早期に治験が開始されるべき	国内治験前	承認審査中	藤本製薬
4	第4回（平成17年4月）	ボルテゾミブ	多発性骨髄腫	早期の承認申請が行われるべき、 承認までの間に安全性確認試験を実施すべき	国内治験中	平成18年10月20日承認、12月1日薬価収載	ヤンセン ファーマ
5	第4回（平成17年4月）	ラロニダーゼ	ムコ多糖症Ⅰ型	早期に治験が開始されるべき。欧米臨床データをもって承認申請を認め、審査期間中に国内治験データの中間報告を求めるなどの柔軟な対応を検討すべき	国内治験前	平成18年10月20日承認、12月1日薬価収載	ジェンザイム・ジャパン
6	第4回（平成17年4月）	ジアゾキサイド	高インスリン血症による低血糖症	早期に治験が開始されるべき	国内治験前	平成20年4月16日承認、6月13日薬価収載	シェリング・プラウ
7	第5回（平成17年7月）	ベバシズマブ	転移性結腸・直腸癌	欧米臨床データ及び国内第Ⅰ相試験データ等を基に早期に承認申請が行われるべき。申請準備期間中及び審査期間中に安全性確認試験が実施されるべき	国内治験中	平成19年4月18日承認、6月8日薬価収載	中外製薬
8	第5回（平成17年7月）	セツキシマブ	転移性結腸・直腸癌	併用療法による第Ⅱ相試験が早期に開始されるべき	国内治験中	平成20年6月17日薬事分科会で報告	メルク
9	第5回（平成17年7月）	エルロチニブ	非小細胞肺癌	進行中の治験状況を注視していくべき	国内治験中	平成19年10月19日承認、12月14日薬価収載	中外製薬
10	第5回（平成17年7月）	テモゾロミド	悪性神経膠腫	国内試験データ（退形成性星細胞腫）及び海外臨床データ（膠芽腫）等を基に早期に承認申請が行われるべき。審査期間中に安全性確認試験（膠芽腫：放射線との併用）が実施されるべき	国内治験終了	平成18年7月26日承認、9月15日薬価収載	シェリング・プラウ
11	第5回（平成17年7月）	ストレプトゾシン	膵島細胞癌	早期に治験が開始されるべき	国内治験前	ライセンス交渉中	（調整中）
12	第6回（平成17年10月）	ガルスルファーゼ	ムコ多糖症Ⅵ型	欧米臨床データをもって承認申請を認め、審査期間中に国内治験データの中間報告を求めるなどの柔軟な対応を検討すべき。学会等の研究班による治療研究によるデータの活用も考慮すべき	国内治験前	平成20年3月28日承認、4月11日薬価収載	アンジェスMG
13	第6回（平成17年10月）	イブリツモマブ チウキセタン	B細胞性非ホジキンリンパ腫	早期に承認申請が行われるべき	国内治験終了	平成20年1月25日承認、6月13日薬価収載	バイエル薬品
14	第6回（平成17年10月）	リポソーマルドキソルビシン	卵巣癌、 AIDS関連カポジ肉腫	早期に承認申請が行われるべき	国内治験中	平成19年1月4日承認、1月19日薬価収載 （AIDS関連カポジ肉腫） 承認審査中（卵巣癌：平成19年1月申請）	ヤンセン ファーマ
15	第6回（平成17年10月）	リファブチン	HIV患者のMAC感染症	早期に承認申請が行われるべき	国内治験中	平成20年6月17日薬事分科会で報告	ファイザー

資料 4

No.	検討会議開催日	成分名	対象疾病	検討会議での主な検討結果	検討当時の状況	現在の状況等	企業名
16	第6回（平成17年10月）	クロファラビン	小児急性リンパ性白血病	早期に治験が開始されるべき	国内治験前	治験準備中（治験計画を関係学会、機構と調整中）	ジェンザイム・ジャパン
17	第7回（平成18年1月）	ネララビン	T細胞性急性リンパ芽球性白血病 T細胞性リンパ芽球性リンパ腫	早期に治験が開始されるべき	国内治験前	平成19年10月19日承認、12月14日薬価収載	グラクソ・スミスクライン
18	第7回（平成18年1月）	ペグアスパラガーゼ	L-アスパラギナーゼに過敏症の急性リンパ性白血病	早期に治験が開始されるべき	国内治験前	導入先と協議中。厚生労働省からも、導入先に早期開発への協力を依頼	（調整中）
19	第7回（平成18年1月）	フェニル酪酸ナトリウム	尿素サイクル異常症	欧米臨床データ及び国内使用症例データ等を基に早期に承認申請が行われるべき。審査期間中に国内治験データ等が収集されるべき	国内治験前	米国企業と導入に向け交渉中	ノーベルファーマ
20	第7回（平成18年1月）	オクスカルバゼピン	てんかん部分発作	早期に治験が開始されるべき	国内治験前	国内開発に着手（開発計画を検討中）	ノバルティスファーマ
21	第8回（平成18年4月）	ポサコナゾール	侵襲性真菌感染症	欧州における臨床試験の状況も見つつ、選択肢を増やすという観点からも、開発が検討されるべき	国内治験前	治験実施中	シェリング・プラウ
22	第8回（平成18年4月）	アバタセプト	中等度・高度の活動性関節リウマチ	進行中の治験を見守るべき	国内治験中	治験実施中	ブリストル・マイヤーズ
23	第8回（平成18年4月）	レナリドミド	骨髄異形成症候群による貧血	早期に治験が開始されるべき。その際には、妊婦・妊娠可能な女性には使用されないようにするなど十分に留意すべき	国内治験前	治験実施中	セルジーン
24	第8回（平成18年4月）	コニバプタン	低ナトリウム血症	我が国における有効性、安全性を注意深く検討しつつ開発を進めるべき	国内治験前	国内開発を断念	アステラス製薬
25	第8回（平成18年4月）	ニチシノン	遺伝性高チロシン血症Ⅰ型	欧米臨床データをもって承認申請を認め、長期の製造販売後調査等で国内情報を収集すべき	国内治験前	国内開発を断念	スウェーデンオーファン
26	第8回（平成18年4月）	アルグルコシダーゼ アルファ	糖原病Ⅱ型（ポンペ病）	日本人患者データを含む欧米臨床データをもって承認申請を認め、長期の製造販売後調査等で国内情報を収集すべき	国内治験前	平成19年4月18日承認、6月8日薬価収載	ジェンザイム・ジャパン
27	第9回（平成18年7月）	スニチニブ	消化管間質腫瘍（イマチニブ耐）、進行性腎細胞癌	欧米臨床データ及び国内第Ⅱ相試験データ等を基に早期に承認申請が行われるべき	国内治験中	平成20年4月16日承認、6月13日薬価収載	ファイザー
28	第9回（平成18年7月）	ソラフェニブ	進行性腎細胞癌	迅速な審査が望まれる	承認審査中	平成20年1月25日承認、4月18日薬価収載	バイエル薬品
29	第9回（平成18年7月）	フォスフェニトイン	てんかん様重積症他	早期に治験が開始されるべき	国内治験前	治験準備中（今秋、開始予定）	ノーベルファーマ
30	第9回（平成18年7月）	デフェラシロクス	輸血による慢性鉄過剰	外国臨床データの活用も考慮した上で、早期に承認申請が行われるべき	国内治験中	平成20年4月16日承認、6月13日薬価収載	ノバルティスファーマ

参考資料　1

「未承認薬使用問題検討会議」開催要綱

1．目的

○　欧米諸国で承認されているが、国内では未承認の医薬品（以下「未承認薬」という。）について、

・　欧米諸国での承認状況及び学会・患者要望を定期的に把握し、

・　臨床上の必要性と使用の妥当性を科学的に検証する

とともに、

・　当該未承認薬について確実な治験実施につなげる

ことにより、その使用機会の提供と安全確保を図ることを目的とする。

2．検討事項

（１）欧米諸国での承認状況の定期的な把握

（２）学会及び患者の要望の定期的な把握

（３）未承認薬の臨床上の必要性と使用の妥当性に関する科学的検証

（４）「企業依頼」及び「医師主導」の治験への振り分けと確実な実施

（５）安全性確認試験の確実な実施　等

3．構成員

○　検討会議の構成員は、がんや循環器等の重篤な疾患領域における薬物療法に関する医学的・薬学的な学識経験を有する者で構成する。

○　検討会議は、構成員のうち１人を座長として選出する。

4．運営

○　検討会議は、年４回定期的に開催するが、必要に応じて随時開催することができる。

○　検討会議は、知的財産権等に係る事項を除き、原則公開するとともに、議事録を作成・公表する。

○　検討会議は、必要に応じて、個別検討事項に係る専門家からなる専門作業班を招集することができる。

5．庶務

○　検討会議の庶務は医薬食品局で行い、医政局及び保険局がこれに協力する。

参考資料　2

「未承認薬使用問題検討会議」

構　成　員

井上　忠夫	国際医療福祉大学大学院　がん薬物療法学分野教授
岩砂　和雄	日本医師会治験促進センター長
大塚　頌子	岡山大学大学院医歯薬学総合研究科教授
川西　徹	国立医薬品食品衛生研究所薬品部長
久保　恵嗣	信州大学医学部内科学第一講座教授
後藤　元	杏林大学医学部教授
佐川　賢一	東京女子医科大学病院薬剤部長
浜田　知久馬	東京理科大学工学部教授
樋口　輝彦	国立精神・神経センター総長
藤原　久義	兵庫県立尼崎病院院長
藤原　康弘	国立がんセンター中央病院臨床検査部長
堀田　知光	独立行政法人国立病院機構名古屋医療センター院長
吉田　茂昭	青森県立中央病院院長

（※　他の専門分野は、必要に応じて適宜参考人として出席を要請。）

参考資料 3

「未承認薬使用問題検討会議」における対象医薬品

類型	概　要
I	平成17年4月以降に欧米4か国（米・英・独・仏）のいずれかの国で承認されたもの
II	過去5年間に学会・患者団体からの要望があり、かつ平成17年3月以前に欧米4か国のいずれかの国で承認されたもの
III	学会・患者団体からの要望はないが、過去2年間に欧米4か国のいずれかの国で承認され、かつ医療上の有用性が高いと考えられるもの

参考資料 4

未承認薬検討会議で検討の対象とする未承認薬の考え方

考え方

適応疾病の重篤性と医療上の有用性とを総合的に評価して選定

（1） 適応疾病の重篤性
以下に分類
① 生命に重大な影響がある疾患（致死的な疾患）
② 病気の進行が不可逆的で、日常生活に著しい影響を及ぼす疾患 等

（2） 医療上の有用性
① 既存の治療法・予防法がない
② 欧米の臨床試験において有効性・安全性等が既存の治療法・予防法と比べて明らかに優れている
③ 欧米において標準的治療法に位置付けられている 等

⇨ 医療上特に必要性が高いと認められるもの

参考資料 5

ワーキンググループの設置について

- ワーキンググループは、がん、小児、循環器の3領域の専門家で構成し、その他の領域（例：精神・神経、臓器移植など）については、品目に応じて、随時専門家を選定する。

- ワーキンググループの専門家は、各領域における医薬品の研究開発及び治験制度に精通した者を座長が指名し、検討会議に報告する。

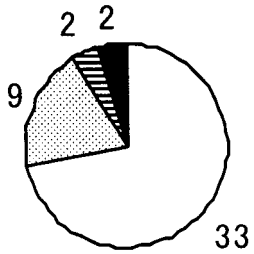
- メンバーは、検討品目に関して関与又は特別の利害関係を有する場合は座長に申し出ることとし、関与等がある場合は、当該品目について発言することができない。

参考資料 6

未承認薬使用問題検討会議での検討状況

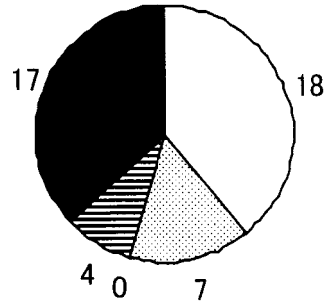
（平成17年1月～：計16回開催）

【検討会議当時の状況】



□ 国内治験前 ▨ 国内治験中 目 国内治験終了 ■ 承認審査中

【現在の状況】（平成20年6月末現在）



□ 治験実施等に向けて検討要請中 ▨ 治験実施中/準備中
▨ 承認申請準備中 目 承認審査中
■ 承認済み

（検討品目の分類）

抗がん剤	22
先天代謝異常症などの小児用薬	11
その他	13
合計	46

資料１－別添１　コニバプタン

平成20年4月4日

厚生労働省医薬食品局審査管理課長　様

アステラス製薬株式会社
代表取締役社長　野木森　雅郁

コニバプタンの国内開発に関する検討結果報告

平成20年2月13日付け薬食審査発第0213002号にてお問い合わせいただきました「未承認薬使用問題検討会議の検討品目に関する取組みについて」以下のようにご回答申し上げます。

記

コニバプタン注射剤は国内において急性心不全の適応取得を目指して臨床試験を実施しておりましたが、十分な効果がみられなかったため、平成12年に国内での臨床試験を中断しておりました。その後、平成17年12月の米国での体液正常型低ナトリウム血症での承認取得、および、平成18年4月の未承認薬使用問題検討会議での勧告を受け、改めて本邦での低ナトリウム血症治療薬としての開発の可能性について検討を開始いたしました。しかしながら、専門家への意見聴取の結果、注射剤の低ナトリウム血症治療の国内での医療ニーズは極めて低いと考えられたため、国内での開発を断念するに至りました。
検討経緯の詳細について以下に述べさせていただきます。

- 平成18年4月に未承認薬使用問題検討会議から以下の勧告を受けた。

  ✓ 「臨床現場のニーズはある程度、近い将来承認される見込みである塩酸モザバプタンによって満たされる可能性がある。但し、注射剤である本剤は意識障害等のある患者等にも投与できるという利点があることから、わが国における有効性、安全性を注意深く検討しつつ開発を進めるべきと考える。」

- 平成17年12月の米国での体液正常型低ナトリウム血症での承認取得、ならびに、平成18年1月に4月の未承認薬使用問題検討会議に本剤が諮る旨の連絡を受けたことにより、国内開発の可能性を検討すべく、循環領域及び内分泌領域の国内専門家（実地医家）に低ナトリウム血症の治療の現況及び医療ニーズに関する意見調査を実施した。その際に聴取した意見は以下の通りで

あった。

- ✓ 血漿ナトリウム濃度が 135mEq/L 以下に低下する低ナトリウム血症の患者は日本でもある程度存在する。
- ✓ しかし、心不全末期の患者にみられる低ナトリウム血症では、血漿ナトリウム濃度の低下はせいぜい 130mEq/L 程度であり、入院下に静脈内投与での治療を要するような重症の低ナトリウム血症の患者は非常に少ない。
- ✓ また、腎不全患者の内、2-3%にみられる低ナトリウム血症の患者の中でも入院治療の対象となるのは 1/10 以下で、意識障害が見られるような重症例はほとんどない。
- ✓ 内分泌領域の患者においても、低ナトリウム血症は軽度であり、投与の簡便な経口投与の薬剤の方が好ましい。本剤のように入院下に短期間の治療に限定されると、投与対象となる患者はほとんどいない。
- ✓ 低ナトリウム血症に対してほとんどの症例では経過観察にて対応しており、治療が必要な時には利尿剤投与と生理食塩水の点滴を行っている。

以上の意見聴取結果より、内分泌領域でのニーズはほとんどなく、心不全あるいは腎不全患者で低ナトリウム血症を併発し治療が必要な本邦の総患者数を、最大で 2 万人～4 万人／年程度と見積もった。

- 平成 18 年 4 月の未承認薬使用問題検討会議からの勧告受領後、同年 7 月に経口バソプレシン拮抗剤である塩酸モザバプタン（フィズリン錠 30mg）が承認された。仮に低ナトリウム血症治療に対するバソプレシン拮抗剤の現場のニーズが高ければ、SIADH に対する治療のみならず他の低ナトリウム血症に対しても既存療法からフィズリン錠 30mg への切り替えが起こると予想された。従って、フィズリン錠 30mg の使用実績よりバソプレシン拮抗剤のニーズがある程度推測できると考え、上記の医師への意見聴取に加えて、フィズリン錠 30mg の処方動向を調査した。
  フィズリン錠 30mg の処方動向を以下に示す。

  - ✓ 2006 年中のフィズリン錠 30mg の販売物量は月当たり 10 錠前後であった。
  - ✓ その後の推移においても大きな増加は無く、直近 1 年間の売上物量は 193 錠であった。
  - ✓ また、発売後から 2008 年 2 月までの累計発売物量も 214 錠であった。

- 以上のように、フィズリン錠 30mg の販売物量は極めて少ないことから、SIADH を含めてもバソプレシン拮抗剤による低ナトリウム血症の治療はほとんど行われていないと推定された。このことより、本邦では低ナトリウム

血症に対しては経過観察あるいは既存療法にて対応しており、バソプレシン拮抗剤などの新規療法へのニーズは極めて低いと考えられた。

- フィズリン錠 30mg が承認された現状では、未承認薬使用問題検討会議の勧告の中でも述べられていたように、本剤の潜在的ニーズは入院患者、特に意識障害等を有する内服不能患者にほぼ限定されると考えられる。しかしながら、専門家への意見聴取結果より、経口投与のできない一部の重症患者を対象とする本剤への医療ニーズは極めて少ないと判断した。
- 以上のように、本邦では注射剤である本剤への医療ニーズは極めて小さいと考えざるを得ず、本邦での開発は困難と結論した。

平成 18 年 4 月の未承認薬使用問題検討会議では、フィズリン錠 30mg（経口剤）承認が見込まれる中で注射剤による低ナトリウム血症治療のニーズも確認すべきとのワーキンググループの答申を受け、コニバプタン注射剤について本邦での開発に関する取組み促進の勧告をいただきました。
しかしながら、前述致しましたようにフィズリン錠 30mg の使用実績より、日本の低ナトリウム血症患者の大部分は経過観察あるいは既存療法で対応されており、バソプレシン拮抗剤へのニーズは低いと推測されたこと、更には、本剤の適応となる経口投与に適さないような重症の低ナトリウム血症の発症はさらに少ないことより、コニバプタン注射剤の医療ニーズは高いとは言い難いと結論いたしました。
また加えて、入院を要するような重症の低ナトリウム血症の患者の数が少ないことより、このような患者を対象とした臨床開発は困難であると考えられることから、弊社としては開発を実施しないこととといたしました。

ただし、上記結論は現時点での判断であり、今後の医療環境の変化などにより、医療現場から強い要望があげられてきた場合には再検討させていただく可能性もあることを申し添えて回答とさせていただきます。

以上

ワーキンググループ検討結果報告書

平成 18 年 4 月 27 日

医薬品名	コニバプタン（米国での販売名：Vaprisol）
概　要	アルギニン・バソプレシン受容体拮抗薬（注射剤）
対象疾病	低ナトリウム血症
外国承認状況	米国（体液正常型の低ナトリウム血症（入院患者））

［対象疾病について］

「体液正常型の低ナトリウム血症」は、脱水や浮腫といった細胞外液量の異常が臨床的に認められない状況における低ナトリウム血症全般を示す。原因疾患としては、抗利尿ホルモン不適合分泌症候群（SIADH）、甲状腺機能低下症、Addison 病、糖質コルチコイド欠乏症に加え、抗利尿ホルモン（ADH）分泌あるいは作用を増強させる薬剤（ニコチン、バルビツール、SSRI を含む各種抗精神病薬など）の影響による場合などがある。さらに SIADH の原因疾患として、肺癌を初めとする悪性腫瘍（特に肺小細胞癌のような ADH 分泌性腫瘍）、頭蓋内病変（腫瘍、出血、炎症など）などが知られているが、特発性の SIADH もみられることがある。すなわち、原因疾患は多岐に渡り、臨床現場では比較的よく観察される病態といえる。なお、わが国では塩酸モザバプタン（大塚製薬）が平成 13 年 8 月に「バソプレシン分泌不適切症候群における低ナトリウム血症の改善」を効能効果として希少疾病用医薬品に指定されていることから、特発性の SIADH については希少疾病と考えて良いと思われる。

「体液正常型の低ナトリウム血症」の治療の基本は原疾患の治療もしくは原因と思われる薬剤の除去である。また、無症状の低ナトリウム血症は飲水制限、利尿薬投与、食塩摂取で治療可能なことが多い。但し、血清ナトリウム濃度が 115mEq/L 以下になると痙攣、昏睡等の中枢神経症状を起こし、適切に治療されないと死に至る場合もあることから、中枢神経症状を伴う重篤あるいは急激な血清ナトリウムの低下を認める場合は、速やかな補正が必要である。

一方、血清ナトリウムの補正にも危険が伴う。血清ナトリウム濃度の急速な上昇（>12mEq/L）は central pontine myelysis（橋中央ミエリン融解）を引き起こし、重篤な神経後遺症を起こすことが報告されている。

［本剤の医療上の有用性について］

本剤は抗利尿ホルモンであるバソプレシンの V1A および V2 受容体のアンタゴニストである。現在、わが国で低ナトリウム血症を効能効果として上市されている医薬品はない。なお、前述の塩酸モザバプタンは非ペプチド性のバソプレシン V2 受容体拮抗薬であり、本剤の同種同効薬といえる。

米国添付文書によると、海外で実施されたプラセボ対照二重盲検試験は、悪性腫瘍、高血圧、急性心筋梗塞等様々な疾患などの種々の基礎疾患による、あるいは原因不明の体液正常型の低ナトリウム血症患者 56 名に対して実施された。治療前血清 Na は 115～130 mEq/L（平均値 124 mEq/L）であった。被験者はプラセボ群（21 名）、本剤 40mg/day（18 名）、本剤 80mg/day（17 名）の 3 群に割り付けられ、それぞれ 4 日間投与された。本剤 40mg/day 群では 52%が、プラセボ群では 28%がそれぞれ血清ナトリウム濃度 4mEq/L 以上の上昇を示し、本剤 40mg/day

群における治療２日目および４日目の血清ナトリウム濃度の上昇はプラセボ群に比べて有意に高かった。また、本剤 20mg/day と 40mg/day のオープンラベル比較試験が実施されたが、20mg/day 群が 11 名に対して 40mg/day 群が 93 群であり、統計解析結果は示されていない。

治験中の有害事象として、投与部位の疼痛、静脈炎等が 15～20%報告された。また、本剤 20～40mg/day を投薬された患者の約 9%に急速な血清ナトリウム濃度の急激な上昇（>12mEq/L）が認められた（神経症状の出現はみられず）。肝機能障害、腎機能障害および高齢者で血中濃度が上昇する可能性が指摘されている。また本剤と CYP3A4 の阻害作用を有する薬剤およびジゴキシンとの相互作用が指摘されている。

なお、本剤のうっ血性心不全患者に対する有効性及び安全性は確立されなかったとの記載が米国添付文書にみられるが、その根拠となるべき詳細データは示されていない。

［検討結果］

本剤は非常に重篤な中枢神経症状を有する体液正常型の低ナトリウム血症の患者に対してナトリウム補正のために短期間(海外治験では４日間)投与する目的で開発、承認された。わが国においては同種同効薬である塩酸モザバプタン（経口剤）が近い将来に承認される見込みであり、本剤とは剤型が異なるものの、臨床現場のニーズはある程度塩酸モザバプタンによって満たされる可能性がある。但し、注射剤である本剤は意識障害等のある患者等にも投与できるという利点があることから、わが国における有効性、安全性を注意深く検討しつつ開発を進めるべきと考える。

資料１－別添２　ニチシノン

平成20年6月26日

厚生労働省医薬食品局
審査管理課長
中 垣 俊 郎 様

未承認薬使用問題検討会議-検討品目ニチシノンに関する取り組みについて
(成分名:ニチシノン・対象疾患:遺伝性高チロシン血症Ⅰ型)

拝啓　平素はお世話になり厚く御礼申し上げます。

弊本社、Swedish Orphan International AB (Stockholm, Sweden)は平成20年7月31日をもって,
スウェーデン・オーファン・インターナショナル株式会社の東京事務所を閉鎖することになりました。

つきましては、薬食審査発第 0213003 号にてお問い合わせがあり、弊社が平成20年3月21日付け書面にてご報告した掲題の件が、本年 7 月末の弊東京事務所閉鎖という事態と関わり、今後どのような方向に進展するのか概略を取りまとめましたのでご報告いたします

敬具

スウェーデン・オーファン・
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別紙

ニチシノンの取り組みの経緯 (Sweden Orphan International AB)

＜国内の遺伝性高チロシン血症Ⅰ型の患者について＞

1. 対象疾患である遺伝性高チロシン血症Ⅰ型の正確な疫学データが存在しない中、日本先天代謝異常学会の専門医の意見を聴取し、当初今後10数年間におよそ10名前後の小児が当疾患に罹患すると推測した。

ところが、平成15年以降今日まで新規患者の報告は無く、この間4大学病院から新生児4症例が当疾患の症状を呈しているとのことで、本剤ニチシノンの緊急提供が弊社に求められた。しかし、いずれの症例も鑑別診断の結果本剤が対象となる遺伝性高チロシン血症Ⅰ型ではなかったと報告された。したがって、未承認薬使用問題検討委員会の検討結果報告書にあるように、現在も国内症例は未だ1例のみである。

＜承認申請に必要な製造販売業者について＞

2. 未承認薬使用問題検討委員会の検討結果報告を受けて、スウェーデン・オーファン・インターナショナル株式会社(本店東京 以下、日本法人)が製造販売業者の認可を取得し、本剤の承認申請を行う可能性を検討した。しかし弊本社が保有する製品リストには、ニチシノンと共に日本で「承認申請」が可能な製品が無く、日本法人が製造販売業者の許可を得ることを断念した。

その後昨年平成19年2月頃まで、日本における「承認申請」のパートナーの候補となる国内製造販売業者の数社と、本剤ニチシノンの導出および承認申請等に関して協議し、当該製造販売業者の意向を本社に報告した。これら国内製造販売業者との協議の中で、対象疾患である遺伝性高チロシン血症Ⅰ型の日本国内の既存患者数(潜在患者数も含めて)が問題になった。現在患者数が1名のみであり、且つ潜在患者数も少なく、本疾患が日本において極めて稀な疾患であることが提携協議の進展がはかばかしくなかった背景と考えられる。本社は、日本の医薬品会社とライセンス・イン/アウトの提携交渉の過程で、ニチシノンの導出先を選定したいという意向を示したがその経過は捗々しくなかった。

＜現在ニチシノンで治療している患者について＞

3. 現在国立香川小児病院にてニチシノンによる治療を受けている男児は、本剤無償提供による治療期間が10年を経過し、本剤は有効で且つ有害事象の報告もなく主治医および患者・家族ともニチシノンによる薬物療法の継続を希望している。しかし、今後何らかの事由により「生体肝移植」により薬物治療から離脱する可能性を否定することはできない。現況を考察すると、日本における本剤の市場性等が極めて不透明であることは多言を要しない。

尚、本年 4 月弊本社が当該無償提供を今後有償提供に変更したい旨、主治医に申し入れたところ本剤の購入は全く不可能との回答があった。日本法人は、「当該患者にはニチシノン療法を将来的にも継続したいが、無償提供されない場合は、生体肝移植の施行を検討する」との主治医の意向を受けて、弊本社と協議した。弊本社は、将来の「承認申請および保険薬価基準収載」に可能性があるならば、それまでの期間は本剤の無償提供を継続することに同意した。

＜今後の取り組みについて＞

4. 弊本社は、欧米における発症率(10 万新生児に約 1 症例)と比べて極めて少ない日本国内の遺伝性高チロシン血症 I 型の患者の発症動向を注視し、近い将来広範な新生児のマス・スクリーニングによって本症の見落が無くなることを期待している。 また、本剤の「承認申請」に関わる国内の製造販売業者の選定および提携については今後とも努力し、可能性がある提携交渉には積極的に対応する所存である。

＜弊東京事務所閉鎖後の Sweden Orphan International AB への連絡先＞

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以上

ワーキンググループ検討結果報告書

平成18年4月27日

医薬品名	ニチシノン（欧米での販売名：Orfadin）
概　要	先天性代謝異常症用薬（経口剤）
対象疾病	遺伝性高チロシン血症Ⅰ型
外国承認状況	米国（遺伝性高チロシン血症Ⅰ型の治療におけるチロシン及びフェニルアラニン摂取制限の補助）、EU（チロシン及びフェニルアラニン摂取制限との併用による遺伝性高チロシン血症Ⅰ型の治療）

［対象疾病について］

遺伝性高チロシン血症Ⅰ型（HT-1）は、チロシン分解酵素のひとつであるフマリルアセト酢酸ヒドラーゼ（FAH）の先天的欠損により、中間代謝産物であるフマリルアセト酢酸やその分解産物であるサクシニルアセトン等の体内濃度が上昇し、肝障害、腎尿細管障害を引き起こす。またサクシニルアセトンがポルフォビリノゲン合成酵素の活性を阻害し、ポルフィリン症を呈する原因になる。最も一般的な経過（全HT-1の80%を占める）は、肝不全の徴候が生後数週から数ヶ月で生じ、2-8ヶ月でその多くが肝不全で死亡する。2ヶ月以前で発症した症例の1年死亡率は60%とされている（Hepatology 20:1187, 1994）。また、生存例では、2歳以降までには肝硬変を呈し、さらに肝細胞癌も合併する場合がある（2歳以上での合併率はWeinberg等によると37%、van Sprosen等によると18%）。その他、症状の進行が緩徐な症例もあるが、大部分の症例は、生命予後不良で、肝移植の適応となる。これまでにわが国で本症と診断された症例はわずか6例である（特殊ミルク情報41:11, 2005）。

［本剤の医療上の有用性について］

本剤は、チロシンの分解に必要な4ヒドロキシフェニルピルビン酸酸化酵素の阻害剤である。この酵素は、チロシン分解酵素カスケードで、HT-1の欠損酵素であるフマリルアセト酢酸ヒドラーゼ（FAH）より上流に位置するため、本剤を投与することによりHT-1の肝腎障害の原因となるフマリルアセト酢酸（FAHの基質）の産生が抑制され治療効果を示す。しかし、本剤の投与では、チロシンの体内濃度を下げることはできないので、チロシン・フェニルアラニンの摂取制限を併用する必要がある。本剤は、チロシン・フェニルアラニンの摂取制限との併用によりHT-1の治療薬として米国で2002年、EUで2005年にそれぞれ承認されている。

評価の対象とされた臨床試験は、スェーデンのSahlgrenska大学病院の医師らを調整医師とするコンパッショネートユースに基づく国際オープン試験（NTBC Study）でありGCP準拠ではない。1991年にニチシノン0.6 mg/kg/dayで開始されたが、1993年からは、1.0 mg/kg/dayを開始用量として適宜増量、と投与量が変更された。1991年2月23日から1997年8月21日に組み入れられた207症例のデータが主な有効性の解析対象であり、開始投与量の増量が各研究者に勧告された後の1993年7月1日から2000年3月28日までに組み入れられた250名の患者のデータが補足的解析の対象とされた。

主要解析における2年及び4年生存率は96%(N=95)、93%(N=35)であった。試験終了後の追跡調査による5年生存率を1994年にvan Spronsenらが行った食事療法単独のHT-1患者の生存率調査（Hepatology 20:1187,1994）と比較したとこ

ろ、治療開始時の年齢が 2 ヶ月未満の群では摂取制限群 28%に対して 82%、2-6 ヶ月の群では 51%に対して 95%と高かった。慢性型が中心と考えられる 6 ヶ月以降に治療開始された群では 5 年生存率にはさほど差がないものの、10 年生存率は 86%と摂取制限群の 59%より高かった。また肝不全等による死亡率も摂取制限群より低かった。

補足的解析では、主に生化学的指標について検討された。90%以上の症例では治療開始 1 週以内に尿中サクシニルアセトン値が正常値に下がり、1 ヶ月以内に全例で正常化したほか、血漿サクシニルアセトン、赤血球ポルフォビリノゲン合成酵素、尿中 5-アミノレブリン酸、α-フェトプロテイン（AFP）、等の値も治療により大幅に改善した。

EMEA における審査の際には、ニチシノンの安全性評価は、NTBC study 以外に、PSUR（市販後の安全性定期報告）のデータ等を含めて評価された。NTBC Study のピボタルな試験 207 症例において認められた有害事象のうち、重篤な事象 49 件の多くは疾患の自然経過に関連し、肝細胞癌、肝不全、肝移植、多臓器不全であり、因果関係を否定出来ない重篤な有害事象は一過性の血小板減少症 3 例のみであった。1991 年 2 月以降 2003 年 12 月 31 日までの製造販売後を含む治療症例 566 名では、肝不全、悪性腫瘍と肝移植以外の重篤な有害事象は 29 症例で認められた。そのうち 2 症例以上で認められたものは、痙攣（6 件）、貧血（2 件）、原因不明の死（4 件）、消化管出血（2 件）、感染症(2 件)、敗血症(2 件)、血小板減少症(3 件)およびポルフィリン症（3 件）であった。痙攣の原因は、発熱（2 件）、低血糖（1 件）、特発性（2 件）、特定不能（1 件）であり、EMEA は痙攣の件数が少ないために因果関係の意義ある評価は出来ないとしている。非重篤の有害事象 145 件のうち多かったのは視覚障害（角膜混濁、角膜症/角膜炎、眼痛、結膜炎など）83 件と血液系の事象（顆粒球減少症、白血球減少症など）17 件であった。これら非重篤の視覚障害もしくは血液系有害事象が理由で治療が中断された症例はなかった。視覚障害は、血中チロシン高値からの二次的現象と考えられており、自然にあるいはチロシン・フェニルアラニンの摂取制限の強化により消失した。

国内では個人輸入により、2 例の日本人 HT-1 患者に対する使用経験が報告されているが、何れも有効とされ、明らかな副作用も報告されていない（特殊ミルク情報 41,23-26,2005 および 41,27-30,2005）。

［検討結果］

本剤は、HT-1 の臨牀症状を改善するのみならず、肝障害の進行をおさえ、生命予後も劇的に改善する。HT-1 に対する他の有効な治療法は肝移植だけであり、ニチシノンは米国・EU で承認されているのみならず、教科書的にも第一選択の非常に有効な治療法となってきている（Nelson Textbook of Pediatrics 17th ed. p402, 2004 等）。

現在、同薬剤の対象となる国内症例は 1 例と国内症例が極端に少ないことを考慮し、欧米での臨床試験データを持って承認申請を認め、承認後は長期にわたる製造販売後調査などで可能な限り国内情報を収集することが望ましいと考える。製薬企業にとっても収益を出しにくいこのような極めてまれな疾患を対象とした薬剤の開発については、海外の小企業が積極的に国内での申請を行えるような対策（たとえば英文の海外承認申請データをそのまま承認申請に使用することを認めるなど）を考慮すべきであると考える。

資料３－① デスベンラファキシン（desvenlafaxine）

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Pristiq™ (desvenlafaxine) Extended-Release Tablets, oral
Initial U.S. Approval: 2008

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Pristiq is not approved for use in pediatric patients (5.1).

INDICATIONS AND USAGE

Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) (1).

DOSAGE AND ADMINISTRATION

- Recommended dose: 50 mg once daily with or without food (2.1).
- There was no evidence that doses greater than 50 mg/day confer any additional benefit (2.1).
- When discontinuing treatment, gradual dose reduction is recommended whenever possible (2.1 and 5.9).
- Tablets should be taken whole; do not divide, crush, chew, or dissolve (2.1).
- Renal Impairment: The recommended dose in patients with moderate renal impairment is 50 mg/day. The recommended dose in patients with severe renal impairment and end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD (2.2).
- Hepatic Impairment: dose escalation above 100 mg/day is not recommended (2.2).

DOSAGE FORMS AND STRENGTHS

Pristiq tablets are available as 50 and 100 mg tablets (3).

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively (3).

CONTRAINDICATIONS

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the Pristiq formulation (4.1).
- Do not use with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping Pristiq before starting an MAOI (4.2).

WARNINGS AND PRECAUTIONS

- **Clinical Worsening/Suicide Risk:** Monitor for clinical worsening and suicide risk (5.1).
- **Serotonin Syndrome:** Serotonin syndrome has been reported with SSRIs and SNRIs (5.2).
- **Elevated Blood Pressure:** Has occurred with Pristiq. Hypertension should be controlled before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- **Abnormal Bleeding:** Pristiq may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation (5. 4).
- **Narrow-angle Glaucoma:** Mydriasis has occurred with Pristiq. Patients with raised intraocular pressure or those at risk of angle-closure glaucoma should be monitored (5.5).
- **Activation of Mania/Hypomania:** Has occurred. Use cautiously in patients with Bipolar Disorder. Caution patients about the risk of activation of mania/hypomania (5.6).
- **Cardiovascular/Cerebrovascular Disease:** Use cautiously in patients with cardiovascular or cerebrovascular disease (5.7).
- **Cholesterol and Triglyceride Elevation:** Have occurred. Use cautiously in patients with lipid metabolism disorders. Consider monitoring serum cholesterol and triglyceride (5.8).
- **Discontinuation Symptoms:** Have occurred. Taper the dose when possible and monitor for discontinuation symptoms (5.9).
- **Renal Impairment:** Reduces the clearance of Pristiq. Dosage adjustment is necessary in severe and ESRD. In moderate renal impairment, the dose should not exceed 50 mg/day (5.10).
- **Seizure:** Can occur. Use cautiously in patients with seizure disorder (5.11).
- **Hyponatremia:** Can occur in association with SIADH (5.12).
- **Drugs Containing Desvenlafaxine or Venlafaxine:** Should not be used concomitantly with Pristiq (5.13).
- **Interstitial Lung Disease and Eosinophilic Pneumonia:** Can occur (5.14).

ADVERSE REACTIONS

Adverse reactions in patients in short-term fixed-dose studies (incidence ≥ 5% and twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Dosage adjustment is recommended in patients with severe renal impairment and end-stage renal disease. The dose should not be escalated in moderate to severe impairment or in ESRD (2.2, 8.6 and 12.6).
- For elderly patients, the possibility of reduced renal clearance of desvenlafaxine should be considered when determining dose (2.2).
- Only administer Pristiq to pregnant or breastfeeding women if the expected benefits outweigh the possible risks (8.1 and 8.3).

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

17.14 Pregnancy
17.15 Nursing
17.16 Residual Inert Matrix Tablet
17.17 FDA-Approved Medication Guide

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

FULL PRESCRIBING INFORMATION:

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*].

1 INDICATIONS AND USAGE

Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) [*see Clinical Studies (14) and Dosage and Administration (2.1)*]. The efficacy of Pristiq has been established in four 8-week, placebo-controlled studies of outpatients who met DSM-IV criteria for major depressive disorder.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for Pristiq is 50 mg once daily, with or without food. In clinical studies, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events and discontinuations were more frequent at higher doses.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9)*].

Pristiq should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

2.2 Special Populations

Pregnant women during the third trimester

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding [*see Use in Specific Populations (8.1)*]. When treating pregnant women with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Pristiq in the third trimester.

Patients with renal impairment

No dosage adjustment is necessary in patients with mild renal impairment (24-hr CrCl = 50-80 mL/min).

The recommended dose in patients with moderate renal impairment (24-hr CrCl = 30-50 mL/min) is 50 mg per day. The recommended dose in patients with severe renal impairment (24-hr CrCl < 30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.6)*].

Patients with hepatic impairment

No adjustment of the starting dosage is necessary for patients with hepatic impairment. However, dose escalation above 100 mg/day is not recommended *[see Clinical Pharmacology (12.6)]*.

Elderly patients

No dosage adjustment is required solely on the basis of age; however, the possibility of reduced renal clearance of Pristiq should be considered when determining the dose [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6)*].

2.3 Maintenance/continuation/extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. However, the longer-term efficacy of Pristiq at the dose of 50 mg/day that was effective in short-term, controlled studies has not been studied. Patients should be periodically reassessed to determine the need for continued treatment.

2.4 Discontinuing Pristiq

Symptoms associated with discontinuation of Pristiq, other SNRIs and SSRIs have been reported [*see Warnings and Precautions (5.9)*]. Patients should be monitored for these symptoms

when discontinuing treatment. A gradual reduction in the dose (by giving 50 mg of Pristiq less frequently) rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

2.5 Switching Patients To or From a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with Pristiq. In addition, at least 7 days must be allowed after stopping Pristiq before starting an MAOI [*see Contraindications (4.2)*].

3 DOSAGE FORMS AND STRENGTHS

Pristiq™ (desvenlafaxine) Extended-Release Tablets are available as 50 and 100 mg tablets.

50 mg, light pink, square pyramid tablet debossed with "W" over "50" on the flat side

100 mg, reddish-orange, square pyramid tablet debossed with "W" over "100" on the flat side

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation.

4.2 Monoamine Oxidase Inhibitors

Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [*see Dosage and Administration (2.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that

antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes

in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.9) and Dosage and Administration (2.3)*] for a description of the risks of discontinuation of Pristiq.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening patients for bipolar disorder

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

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with Pristiq treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea).

The concomitant use of Pristiq and MAOIs is contraindicated [*see Contraindications (4.2)*].

If concomitant treatment with Pristiq and an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Pristiq with serotonin precursors (such as tryptophan supplements) is not recommended.

5.3 Elevated Blood Pressure

Patients receiving Pristiq should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq.

Sustained hypertension

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [*see Adverse Reactions (6.1)*]. Treatment with Pristiq at all doses from 50 mg/day to 400 mg/day in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) $\geq$ 90 mm Hg and $\geq$ 10 mm Hg above baseline for 3 consecutive on-therapy visits (see Table 2). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a consistent increase in the proportion of subjects who developed sustained hypertension. This was seen at all doses with a suggestion of a higher rate at 400 mg/day.

Table 2: Proportion of Patients with Sustained Elevation of Supine Diastolic Blood Pressure

Treatment Group	Proportion of Patients with Sustained Hypertension
Placebo	0.5%
Pristiq 50 mg/day	1.3%
Pristiq 100 mg/day	0.7%
Pristiq 200 mg/day	1.1%
Pristiq 400 mg/day	2.3%

5.4 Abnormal Bleeding

SSRIs and SNRIs, including Pristiq, may increase the risk of bleeding events. Concomitant use of aspirin, , nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have

demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Narrow-angle Glaucoma

Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

5.6 Activation of Mania/Hypomania

During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania.

5.7 Cardiovascular/Cerebrovascular Disease

Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*]. Increases in blood pressure and small increases in heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies.

5.8 Serum Cholesterol and Triglyceride Elevation

Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [*see Adverse Reactions (6.1)*].

5.9 Discontinuation of Treatment with Pristiq

Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy.

During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia,

hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [*see Dosage and Administration (2.4) and Adverse Reactions (6.1)*].

5.10 Renal Impairment

In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [*see Clinical Pharmacology (12.6)*]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [*see Dosage and Administration (2.2)*].

5.11 Seizure

Cases of seizure have been reported in pre-marketing clinical studies with Pristiq. Pristiq has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical studies. Pristiq should be prescribed with caution in patients with a seizure disorder.

5.12 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6)*]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.13 Co-administration of Drugs Containing Desvenlafaxine and Venlafaxine

Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq.

5.14 Interstitial Lung Disease and Eosinophilic Pneumonia

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

6 ADVERSE REACTIONS

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

- Hypersensitivity [*see Contraindications (4.1)*]
- Effects on blood pressure [*see Warnings and Precautions (5.3)*]
- Abnormal bleeding [*see Warnings and Precautions (5.4)*]
- Mydriasis [*see Warnings and Precautions (5.5)*]
- Hypomania and mania [*see Warnings and Precautions (5.6)*]
- Serum cholesterol and triglyceride elevation [*see Warnings and Precautions (5.8)*]
- Seizure [*see Warnings and Precautions (5.11)*]

6.1 Clinical Studies Experience

The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥ 5% and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Adverse reactions reported as reasons for discontinuation of treatment

Combined across 8-week placebo-controlled pre-marketing studies for major depressive disorder, 12% of the 1,834 patients who received Pristiq (50-400 mg) discontinued treatment due to an adverse experience, compared with 3% of the 636 placebo-treated patients in those studies. At the recommended dose of 50 mg, the discontinuation rate due to an adverse experience for Pristiq (4.1%) was similar to the rate for placebo (3.8%). For the 100 mg dose of Pristiq the discontinuation rate due to an adverse experience was 8.7%.

The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were: nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%).

Patient exposure

Pristiq was evaluated for safety in 3,292 patients diagnosed with major depressive disorder who participated in multiple-dose pre-marketing studies, representing 1,289 patient-years of exposure. Among these 3,292 Pristiq-treated patients, 1,834 patients were exposed to Pristiq in 8-week, placebo-controlled studies at doses ranging from 50 to 400 mg/day. Out of the 1,834

patients, 687 Pristiq-treated patients continued into a 10-month open-label study. Of the total 3,292 patients exposed to at least one dose of Pristiq, 1,070 were exposed to Pristiq for 6 months, representing 842 patient-years of exposure, and 274 were exposed for one year, representing 241 patient-years of exposure.

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

Common adverse reactions in placebo-controlled MDD studies

Table 3 shows the incidence of common adverse reactions that occurred in ≥ 2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed dose, pre-marketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment.

Table 3: Common Adverse Reactions: Percentage of Patients (≥ 2% in any Fixed-Dose Group) in MDD 8-Week Placebo-Controlled Studies[a]

	Percentage of Patients Reporting Reaction				
		Pristiq			
System Organ Class **Preferred Term**	**Placebo**	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Cardiac disorders					
Palpitations	2	1	3	2	3
Tachycardia	1	1	<1	1	2
Blood pressure increased	1	1	1	2	2
Gastrointestinal disorders					
Nausea	10	22	26	36	41
Dry mouth	9	11	17	21	25
Diarrhea	9	11	9	7	5
Constipation	4	9	9	10	14
Vomiting	3	3	4	6	9
General disorders and administration site conditions					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
Asthenia	1	1	2	1	1
Metabolism and nutrition disorders					
Decreased appetite	2	5	8	10	10
Weight decreased	1	2	1	1	2
Nervous system disorders					
Dizziness	5	13	10	15	16

Table 3: Common Adverse Reactions: Percentage of Patients (≥ 2% in any Fixed-Dose Group) in MDD 8-Week Placebo-Controlled Studies[a]

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction				
		Pristiq			
	Placebo	50 mg	100 mg	200 mg	400 mg
Somnolence	4	4	9	12	12
Headache	23	20	22	29	25
Tremor	2	2	3	9	9
Paraesthesia	1	2	2	1	3
Disturbance in attention	<1	<1	1	2	1
Psychiatric disorders					
Insomnia	6	9	12	14	15
Anxiety	2	3	5	4	4
Nervousness	1	<1	1	2	2
Irritability	1	2	2	2	2
Abnormal dreams	1	2	3	2	4
Renal and urinary disorders					
Urinary hesitation	0	<1	1	2	2
Respiratory, thoracic and mediastinal disorders					
Yawning	<1	1	1	4	3
Skin and subcutaneous tissue disorders					
Hyperhidrosis	4	10	11	18	21
Rash	<1	1	1	2	<1
Special Senses					
Vision blurred	1	3	4	4	4
Mydriasis	<1	2	2	6	6
Tinnitus	1	2	1	1	2
Dysguesia	1	1	1	1	2
Vascular disorders					
Hot flush	<1	1	1	2	2

a: Percentage based on the number of patients (placebo, n = 636; Pristiq 50 mg, n = 317; Pristiq 100 mg, n = 424; Pristiq 200 mg, n = 307; Pristiq 400 mg, n = 317).

Sexual function adverse reactions

Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥ 2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, pre-marketing clinical studies).

Table 4: Sexual Function Disorders: Adverse Reactions (≥ 2% in Men[a] or Women[b] in any Pristiq Group) During the On-Therapy Period

System Organ Class Preferred Term	Placebo	Pristiq 50 mg	Pristiq 100 mg	Pristiq 200 mg	Pristiq 400 mg
Men only					
Anorgasmia	0	0	3	5	8
Libido decreased	1	4	5	6	3
Orgasm abnormal	0	0	1	2	3
Ejaculation delayed	<1	1	5	7	6
Erectile dysfunction	1	3	6	8	11
Ejaculation disorder	0	0	1	2	5
Ejaculation failure	0	1	0	2	2
Sexual dysfunction	0	1	0	0	2
Women only					
Anorgasmia	0	1	1	0	3

a: Percentage based on the number of men (placebo, n = 239; Pristiq 50 mg, n = 108; Pristiq 100 mg, n = 157; Pristiq 200 mg, n = 131; Pristiq 400 mg, n = 154).
b: Percentage based on the number of women (placebo, n = 397; Pristiq 50 mg, n = 209; Pristiq 100 mg, n = 267; Pristiq 200 mg, n = 176; Pristiq 400 mg, n = 163).

Other adverse reactions observed in pre-marketing clinical studies

Other infrequent adverse reactions, not described elsewhere, occurring at an incidence of < 2% in MDD patients treated with Pristiq were:

Immune system disorders – Hypersensitivity.

Investigations – Liver function test abnormal, blood prolactin increased.

Nervous system disorders – Convulsion, syncope, extrapyramidal disorder.

Psychiatric disorders – Depersonalization, hypomania.

Respiratory, thoracic and mediastinal disorders – Epistaxis.

Vascular disorders – Orthostatic hypotension.

In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients

experienced these events during Pristiq treatment as compared to placebo [*see Warnings and Precautions (5.7)*].

Discontinuation events

Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥ 5% include: dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9)*].

Laboratory, ECG and vital sign changes observed in MDD clinical studies

The following changes were observed in placebo-controlled, short term, pre-marketing MDD studies with Pristiq.

Lipids

Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [*see Warnings and Precautions (5.8)*].

The percentage of patients who exceeded a predetermined threshold value is shown in Table 5.

Table 5: Incidence (%) of Patients With Lipid Abnormalities of Potential Clinical Significance*

		Pristiq			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Total Cholesterol *(Increase of ≥ 50 mg/dl and an absolute value of ≥ 261 mg/dl)	2	3	4	4	10
LDL Cholesterol *(Increase ≥ 50 mg/dl and an absolute value of ≥ 190 mg/dl)	0	1	0	1	2
Triglycerides, fasting *(Fasting: ≥ 327 mg/dl)	3	2	1	4	6

Proteinuria

Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6). This proteinuria was not associated with increases in BUN or creatinine and was generally transient.

Table 6: Incidence (%) of Patients with Proteinuria in the Fixed-dose Clinical Studies

		Pristiq			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Proteinuria	4	6	8	5	7

ECG changes

Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval.

Vital sign changes

Table 7 summarizes the changes that were observed in placebo-controlled, short-term, pre-marketing studies with Pristiq in patients with MDD (doses 50 to 400 mg).

Table 7: Mean Changes in Vital Signs at Final on Therapy for All Short-term, Fixed-dose Controlled Studies

		Pristiq			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Blood pressure					
Supine systolic bp (mm Hg)	-1.4	1.2	2.0	2.5	2.1
Supine diastolic bp (mm Hg)	-0.6	0.7	0.8	1.8	2.3
Pulse rate					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
Weight (kg)	0.0	-0.4	-0.6	-0.9	-1.1

At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight change between Pristiq- and placebo-treated patients.

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents

The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*].

7.2 Monoamine Oxidase Inhibitors (MAOI)

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on

antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*].

7.3 Serotonergic Drugs

Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is co-administered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*].

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

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

7.5 Ethanol

A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq.

7.6 Potential for Other Drugs to Affect Desvenlafaxine

Inhibitors of CYP3A4 (ketoconazole)

CYP3A4 is a minor pathway for the metabolism of Pristiq. In a clinical study, ketoconazole (200 mg BID) increased the area under the concentration vs. time curve AUC of Pristiq (400 mg single dose) by about 43% and C_{max} by about 8%. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq.

Inhibitors of other CYP enzymes

Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq.

7.7 Potential for Desvenlafaxine to Affect Other Drugs

Drugs metabolized by CYP2D6 (desipramine)

In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6.

Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. When desvenlafaxine succinate was administered at a dose of 100 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the C_{max} and AUC of desipramine increased approximately 25% and 17%,

respectively. When 400 mg (8 times the recommended 50 mg dose) was administered, the C_{max} and AUC of desipramine increased approximately 50% and 90%, respectively. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug.

Drugs metabolized by CYP3A4 (midazolam)

In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme.

In a clinical study, Pristiq 400 mg daily (8 times the recommended 50 mg dose) was co-administered with a single 4 mg dose of midazolam (a CYP3A4 substrate). The AUC and C_{max} of midazolam decreased by approximately 31% and 16%, respectively. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug.

Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19

In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes.

7.8 P-glycoprotein Transporter

In vitro, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter.

The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter.

7.9 Electroconvulsive Therapy

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Teratogenic effects – Pregnancy Category C

When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity in rats at any doses tested, up to 10 times a human dose of 100 mg/day (on a mg/m^2 basis) in rats, and up to 15 times the a human dose of 100 mg/day (on a mg/m^2 basis) in rabbits. However, fetal weights were decreased in rats, with a no-effect dose 10 times a human dose of 100 mg/day (on a mg/m^2 basis).

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation. The cause of these deaths is not known. The no-effect dose for rat pup

mortality was 10 times a human dose of 100 mg/day (on a mg/m^2 basis). Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine at a dose 29 times a human dose of 100 mg/day (on a mg/m^2 basis).

There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks.

Non-teratogenic effects

Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*].

8.2 Labor and Delivery

The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks.

8.3 Nursing Mothers

Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [*see Box Warning* and *Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need.

8.5 Geriatric Use

Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered.

SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS, Hyponatremia).

8.6 Renal Impairment

In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*].

8.7 Hepatic Impairment

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Desvenlafaxine is not a controlled substance.

9.2 Abuse and Dependence

Although Pristiq has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies. However, it is not possible to predict on the basis of pre-marketing experience, the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Pristiq (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience with Overdosage

There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In pre-marketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported.

Among the patients included in the MDD pre-marketing studies of Pristiq, there were four adults who ingested desvenlafaxine succinate (4000 mg [desvenlafaxine alone], 900, 1800 and 5200 mg [in combination with other drugs]); all patients recovered. In addition, one patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine succinate, was treated, and recovered. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included: headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia.

Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert.

In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear.

Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

10.2 Management of Overdosage

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered.

Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known.

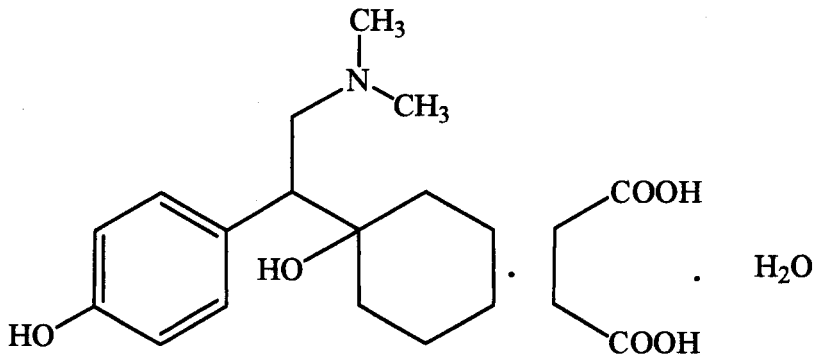
In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

11 DESCRIPTION

Pristiq is an extended-release tablet for oral administration that contains desvenlafaxine succinate, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a

medication used to treat major depressive, generalized anxiety, social anxiety and panic disorders.

Desvenlafaxine is designated *RS*-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of $C_{16}H_{25}NO_2$ (free base) and $C_{16}H_{25}NO_2 \cdot C_4H_6O_4 \cdot H_2O$ (succinate monohydrate). Desvenlafaxine succinate monohydrate has a molecular weight of 399.48. The structural formula is shown below.



Desvenlafaxine succinate is a white to off-white powder that is soluble in water. The solubility of desvenlafaxine succinate is pH dependent. Its octanol:aqueous system (at pH 7.0) partition coefficient is 0.21.

Pristiq is formulated as an extended-release tablet for once-a-day oral administration.

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively.

Inactive ingredients consist of hypromellose, microcrystalline cellulose, talc, magnesium stearate and film coating, which consists of sodium carboxymethylcellulose, maltodextrin, dextrose, titanium dioxide, stearic acid and iron oxide(s).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Non-clinical studies have shown that desvenlafaxine succinate is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI). The clinical efficacy of desvenlafaxine succinate is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

12.2 Pharmacodynamics

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pristiq also lacked monoamine oxidase (MAO) inhibitory activity.

12.3 Pharmacokinetics

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. The mean terminal half-life, $t_{1/2}$, is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

12.4 Absorption and Distribution

The absolute oral bioavailability of Pristiq after oral administration is about 80%. Mean time to peak plasma concentrations (T_{max}) is about 7.5 hours after oral administration.

A food-effect study involving administration of Pristiq to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the C_{max} was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, Pristiq can be taken without regard to meals [*see Dosage and Administration (2.1)*].

The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. The desvenlafaxine volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

12.5 Metabolism and Elimination

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and < 5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

12.6 Special Populations

Age

In a study of healthy subjects administered doses of up to 300 mg, there was an approximate 32% increase in C_{max} and a 55% increase in AUC in subjects older than 75 years of age (n = 17), compared with subjects 18 to 45 years of age (n = 16). Subjects 65 to 75 years of age (n = 15) had no change in C_{max}, but an approximately 32% increase in AUC, compared to subjects 18 to 45 years of age [*see Dosage and Administration (2.2)*].

Gender

In a study of healthy subjects administered doses up to of 300 mg, women had an approximately 25% higher C_{max} and an approximately 10% higher AUC than age-matched men. No adjustment of dosage on the basis of gender is needed.

Race

Pharmacokinetic analysis showed that race (White, n = 466; Black, n = 97; Hispanic, n = 39; Other, n = 33) had no apparent effect on the pharmacokinetics of Pristiq. No adjustment of dosage on the basis of race is needed.

Hepatic insufficiency

The disposition of desvenlafaxine succinate after administration of 100 mg was studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and to healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were similar in subjects with mild hepatic impairment and healthy subjects (< 5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (< 5% difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

Renal insufficiency

The disposition of desvenlafaxine after administration of 100 mg was studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) (n = 9) requiring dialysis and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Increases in AUCs of about 42% in mild renal impairment (24-hr CrCl = 50-80 mL/min), about 56% in moderate renal impairment (24-hr CrCl = 30-50 mL/min), about 108% in severe renal impairment (24-hr CrCl ≤ 30 mL/min), and about 116% in ESRD subjects were observed, compared with healthy, age-matched control subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the control subjects to approximately 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively. Less than 5% of the drug in the body was cleared during a standard 4-hour hemodialysis procedure.

Dosage adjustment (every other day dosing) is recommended in patients with significant impairment of renal function [*see Dosage and Administration (2.2) and Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Desvenlafaxine succinate administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumors in either study.

Mice received desvenlafaxine succinate at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The 300 mg/kg/day dose is 15 times a human dose of 100 mg/day on a mg/m^2 basis.

Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose is 29 (males) or 48 (females) times a human dose of 100 mg/day on a mg/m^2 basis.

Mutagenesis

Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

Impairment of fertility

Reduced fertility was observed in a study in which both male and female rats received desvenlafaxine succinate. This effect was noted at oral doses approximately 10 times a human dose of 100 mg/day on a mg/m^2 basis. There was no effect on fertility at oral doses approximately 3 times a human dose of 100 mg/day on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of Pristiq as a treatment for depression was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies (at doses of 50 mg/day to 400 mg/day) in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder. In the first study, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of Pristiq once daily, or placebo (n = 118). In a second study, patients received either 200 mg (n = 121) or 400 mg (n = 124) of Pristiq once daily, or placebo (n = 124). In two additional studies, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of Pristiq once daily, or placebo (n = 150 and n = 161).

Pristiq showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score in four studies and overall improvement, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg/day and 100 mg/day there was no suggestion of a greater effect with the higher dose *[see Dosage and Administration (2.1)]*. Overall, while adverse events and discontinuations were more frequent at higher doses, no severe toxicity was observed.

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

Pristiq™ (desvenlafaxine) Extended-Release Tablets are available as follows:

50 mg, light pink, square pyramid tablet debossed with "W" (over) "50" on the flat side

NDC 0008-1211-14, bottle of 14 tablets.

NDC 0008-1211-30, bottle of 30 tablets.

NDC 0008-1211-01, bottle of 90 tablets.

NDC 0008-1211-50, 10 blisters of 10 (HUD).

100 mg, reddish-orange, square pyramid tablet debossed with "W" (over) "100" on the flat side

NDC 0008-1222-14, bottle of 14 tablets.

NDC 0008-1222-30, bottle of 30 tablets.

NDC 0008-1222-01, bottle of 90 tablets.

NDC 0008-1222-50, 10 blisters of 10 (HUD).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Each tablet contains 76 or 152 mg of desvenlafaxine succinate equivalent to 50 or 100 mg of desvenlafaxine, respectively.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

U.S. Patent No. 6,673,838.

17 PATIENT COUNSELING INFORMATION

Advise patients, their families, and their caregivers about the benefits and risks associated with treatment with Pristiq and counsel them in its appropriate use.

Advise patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document [*see Patient Counseling Information (17.17)*].

17.1 Suicide Risk

Advise patients, their families and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

17.2 Concomitant Medication

Advise patients taking Pristiq not to use concomitantly other products containing desvenlafaxine or venlafaxine. Healthcare professionals should instruct patients not to take Pristiq with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping Pristiq before starting an MAOI [*see Contraindications (4.2)*].

17.3 Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of Pristiq and triptans, tramadol, tryptophan supplements or other serotonergic agents [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

17.4 Elevated Blood Pressure

Advise patients that they should have regular monitoring of blood pressure when taking Pristiq [*see Warnings and Precautions (5.3)*].

17.5 Abnormal Bleeding

Patients should be cautioned about the concomitant use of desvenlafaxine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. [*see Warnings and Precautions (5.4)*].

17.6 Narrow-angle Glaucoma

Advise patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) that mydriasis has been reported and they should be monitored [*see Warnings and Precautions (5.5)*].

17.7 Activation of Mania/Hypomania

Advise patients, their families and caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.6)*].

17.8 Cardiovascular/Cerebrovascular Disease

Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1) and Warnings and Precautions (5.7)*].

17.9 Serum Cholesterol and Triglyceride Elevation

Advise patients that elevations in total cholesterol, LDL and triglycerides may occur and that measurement of serum lipids may be considered [*see Warnings and Precautions (5.8)*].

17.10 Discontinuation

Advise patients not to stop taking Pristiq without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping Pristiq [*see Warnings and Precautions (5.9) and Adverse Reactions (6.1)*].

17.11 Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that Pristiq therapy does not adversely affect their ability to engage in such activities.

17.12 Alcohol

Advise patients to avoid alcohol while taking Pristiq [*see Drug Interactions (7.5)*].

17.13 Allergic Reactions

Advise patients to notify their physician if they develop allergic phenomena such as rash, hives, swelling, or difficulty breathing.

17.14 Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy [*see Use in Specific Populations (8.1)*].

17.15 Nursing

Advise patients to notify their physician if they are breastfeeding an infant [*see Use in Specific Populations (8.3)*].

17.16 Residual Inert Matrix Tablet

Patients receiving Pristiq may notice an inert matrix tablet passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

17.17 FDA-Approved Medication Guide

MEDICATION GUIDE

Pristiq™ (pris-**TEEK**) Extended-Release Tablets

(desvenlafaxine)

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **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) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- 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.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- 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	• trouble sleeping (insomnia)
• attempts to commit suicide	• new or worse irritability
• new or worse depression	• acting aggressive, being angry, or violent
• new or worse anxiety	• acting on dangerous impulses
• feeling very agitated or restless	• an extreme increase in activity and talking (mania)
• panic attacks	• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Important Information about Pristiq

Read the patient information that comes with Pristiq before you take Pristiq and each time you refill your prescription. There may be new information. If you have questions, ask your healthcare provider. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Pristiq?

- Pristiq is a prescription medicine used to treat depression. Pristiq belongs to a class of medicines known as SNRIs (or serotonin-norepinephrine reuptake inhibitors).
- Pristiq has not been studied orapproved for use in children and adolescents.

Who should not take Pristiq?

Do not take Pristiq if you:

- are allergic to desvenlafaxine, venlafaxine or any of the ingredients in Pristiq. See the end of this Medication Guide for a complete list of ingredients in Pristiq.
- currently take or have taken within the last 14 days, any medicine known as an MAOI. Taking an MAOI with certain other medicines, including Pristiq, can cause serious or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking Pristiq before you take any MAOI.

What should I tell my healthcare provider before taking Pristiq?

Tell your healthcare provider about all your medical conditions, including if you:

- have high blood pressure.
- have heart problems.
- have high cholesterol or high triglycerides.
- have a history of a stroke.

- have glaucoma.
- have kidney problems.
- have liver problems.
- have or had bleeding problems.
- have or had seizures or convulsions.
- have mania or bipolar disorder.
- have low sodium levels in your blood.
- are pregnant or plan to become pregnant. It is not known if Pristiq will harm your unborn baby.
- are breastfeeding. Pristiq can pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take Pristiq.

Serotonin syndrome

A rare but potentially life-threatening condition called serotonin syndrome can happen when medicines such as Pristiq are taken with certain other medicines. Serotonin syndrome can cause serious changes in how your brain, muscles and digestive system work. **Especially tell your healthcare provider if you take the following:**

- medicines to treat migraine headaches known as triptans
- medicines used to treat mood disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs)
- silbutramine
- tramadol
- St. John's Wort
- MAOIs (including linezolid, an antibiotic)
- tryptophan supplements

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before you take Pristiq with any of these medicines, talk to your healthcare provider about serotonin syndrome. See "What are the possible side effects of Pristiq?"

Pristiq contains the medicine desvenlafaxine. Do not take Pristiq with other medicines containing venlafaxine or desvenlafaxine.

How should I take Pristiq?

- Take Pristiq exactly as your healthcare provider has told you.
- Take Pristiq at about the same time each day.
- Pristiq may be taken either with or without food.
- Swallow Pristiq tablets whole with fluid. Do not crush, cut, chew, or dissolve Pristiq tablets because the tablets are time released.
- When you take Pristiq, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.

- It is common for antidepressant medicines such as Pristiq to take several weeks before you start to feel better. Do not stop taking Pristiq if you do not feel results right away.
- Do not stop taking or change the dose of Pristiq without talking with your healthcare provider, even if you feel better.
- Talk with your healthcare provider about how long you should use Pristiq. Take Pristiq for as long as your healthcare provider tells you to.
- If you miss a dose of Pristiq, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do not try to "make up" for the missed dose by taking two doses at the same time.
- Do not take more Pristiq than prescribed by your healthcare provider. If you take more Pristiq than the amount prescribed, contact your healthcare provider right away.
- In case of an overdose of Pristiq, call your healthcare provider or poison control center, or go to the emergency room right away.

What should I avoid while taking Pristiq?

- Do not drive a car or operate machinery until you know how Pristiq affects you.
- Avoid drinking alcohol while taking Pristiq.

What are the possible side effects of Pristiq?

Pristiq can cause serious side effects including:

- **See the beginning of this Medication Guide - Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions.**
- **Serotonin syndrome. See "What should I tell my healthcare provider before taking Pristiq?"**

  Get medical help right away if you think that you have serotonin syndrome. Signs and symptoms of serotonin syndrome may include one or more of the following:

  - restlessness
  - hallucinations (seeing and hearing things that are not real)
  - loss of coordination
  - fast heart beat
  - increased body temperature
  - increase in blood pressure
  - diarrhea
  - coma
  - nausea
  - vomiting

- **Pristiq may also cause other serious side effects including:**
- **New or worsened high blood pressure (hypertension)** Your healthcare provider should monitor your blood pressure before and while you are taking Pristiq. If you have high blood pressure, it should be controlled before you start taking Pristiq.
- **Abnormal bleeding or bruising** Pristiq and other SNRIs/ SSRIs may cause you to have an increased chance of bleeding. Taking aspirin, NSAIDs (non-steroidal anti-

inflammatory drugs), or blood thinners may add to this risk. Tell your healthcare provider right away about any unusual bleeding or bruising.

- **Glaucoma (increased eye pressure)**
- **Increased cholesterol and triglyceride levels in your blood**
- **Symptoms when stopping Pristiq (discontinuation symptoms)** Side effects may occur when stopping Pristiq (discontinuation symptoms), especially when therapy is stopped suddenly. Your healthcare provider may want to decrease your dose slowly to help avoid side effects. Some of these side effects may include:
  - dizziness
  - nausea
  - headache
  - irritability
  - sleeping problems (insomnia)
  - anxiety
  - abnormal dreams
  - tiredness
  - sweating
  - diarrhea
- **Seizures (convulsions)**
- **Low sodium levels in your blood** (Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. In severe or more sudden cases, symptoms can include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels could be fatal.)

Contact your healthcare provider if you think you have any of these side effects.

Common side effects with Pristiq include:

- nausea
- headache
- dry mouth
- sweating
- dizziness
- insomnia
- constipation
- loss of appetite
- sleepiness
- tiredness
- diarrhea
- vomiting
- anxiety
- tremor
- dilated pupils
- decreased sex drive
- delayed orgasm and ejaculation

These are not all the possible side effects of Pristiq. Tell your healthcare provider about any side effect that bothers you or does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information on these and other side effects associated with Pristiq, talk to your healthcare provider visit our web site at www.pristiq.com or call our toll-free number 1-888-Pristiq.

How should I store Pristiq?

- Store Pristiq at 68° to 77°F (20° to 25°C)

- Do not use Pristiq after the expiration date (EXP), which is on the container. The expiration date refers to the last day of that month.
- Keep Pristiq and all medicines out of the reach of children.

General Information about the safe and effective use of Pristiq

Medicines are sometimes used for conditions that are not mentioned in Medication Guides. Do not use Pristiq for a condition for which it was not prescribed. Do not give Pristiq to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Pristiq. If you would like more information, talk with your healthcare provider. You can ask you pharmacist or healthcare provider for information about Pristiq that is written for healthcare professionals. For more information, go to www.pristiq.com or call 1-888-Pristiq (774-7847).

What are the ingredients in Pristiq?

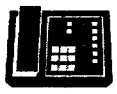
Active ingredient: desvenlafaxine
Inactive ingredients: hypromellose, microcrystalline cellulose, talc, magnesium stearate, a film coating which consists of sodium carboxymethylcellulose, maltodextrin, dextrose, titanium dioxide, stearic acid and iron oxide(s).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued February 2008

Contact Information
Please visit our web site at www.pristiq.com, or call our toll-free number 1-888-Pristiq to receive more information.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.



Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

W#
ET01
Rev 02/08

資料３－② ベンダムスチン（bendamustine）

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TREANDA (bendamustine hydrochloride) for Injection, for intravenous infusion
Initial U.S. Approval: 2008

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

TREANDA for Injection is an alkylating drug indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. (1)

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

- 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.1)
- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity (2.2)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m^2 on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m^2 on Days 1 and 2. (2.2)
- Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle. (2.2)
- Dose re-escalation may be considered. (2.2)
- TREANDA for Injection must be reconstituted and further diluted prior to infusion. (2.3)

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

TREANDA for Injection single-use vial containing 100 mg of bendamustine HCl as lyophilized powder (3)

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

- Known hypersensitivity to bendamustine or mannitol (4)

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

- Myelosuppression: May warrant treatment delay or dose reduction. Monitor closely and restart treatment based on ANC and platelet count recovery. (5.1)
- Infections: Monitor for fever and other signs of infection and treat promptly. (5.2)
- Infusion Reactions and Anaphylaxis: Severe anaphylactic reactions have occurred. Monitor clinically and discontinue drug for severe reactions. Ask patients about reactions after the first cycle. Consider pre-treatment for cycles subsequent to milder reactions. (5.3)
- Tumor Lysis Syndrome: May lead to acute renal failure and death. Take precautions in patients at high risk. (5.4)
- Skin Reactions: Discontinue for severe skin reactions. (5.5)
- Use in Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TREANDA. (5.6, 8.1)

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

Most common adverse reactions (frequency ≥15%) are neutropenia, pyrexia, thrombocytopenia, nausea, anemia, leukopenia, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cephalon, Inc., at 1-800-896-5855 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine. (7)

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

- Renal impairment: Do not use if CrCL is <40 mL/min. Use with caution in lesser degrees of renal impairment. (8.6)
- Hepatic impairment: Do not use in moderate or severe hepatic impairment. Use with caution in mild hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TREANDA® (bendamustine hydrochloride) for Injection is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

TREANDA is intended for administration as an intravenous infusion over 30 minutes. The recommended dose is 100 mg/m^2 administered intravenously on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Consider using allopurinol as prevention for patients at high risk of tumor lysis syndrome for the first few weeks of treatment.

2.2 Dose Delays, Dose Modifications and Reinitiation of Therapy

TREANDA administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. Dose delays may be warranted. *[See Warnings and Precautions (5.1)]*

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

2.3 Reconstitution/Preparation for Intravenous Administration

- Aseptically reconstitute each 100 mg TREANDA vial with 20 mL of Sterile Water for Injection, USP. This yields a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used.

- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

- Sterile Water for Injection, USP and 0.9% Sodium Chloride Injection, USP must be used as outlined above. Compatibility with other diluents has not been determined.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

2.4 Admixture Stability

TREANDA contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

Once diluted with 0.9% Sodium Chloride Injection, USP, the final admixture, is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of TREANDA must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

TREANDA for Injection single-use vial containing 100 mg of bendamustine HCl as white to off-white lyophilized powder.

4 CONTRAINDICATIONS

TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. *[See Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with TREANDA are likely to experience myelosuppression. In the randomized CLL clinical study, patients receiving TREANDA experienced Grade 3 or 4 neutropenia (24%), febrile neutropenia (3%), red blood cell transfusions (20%), and platelet transfusions (< 1%). In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the randomized CLL clinical study hemoglobin and WBC differential counts were monitored weekly and platelet counts were monitored each cycle. Based on data from this study, hematologic nadirs should be expected in the third week of therapy and may require dose delays if recovery to the recommended values have not occurred by day 28.

Prior to the initiation of the next cycle of therapy, the ANC should be ≥ 1 x 10^9/L and the platelet count should be ≥ 75 x 10^9/L.

5.2 Infections

Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections. Patients with myelosuppression following TREANDA treatment should be advised to contact a physician if they have symptoms or signs of infection.

5.3 Infusion Reactions and Anaphylaxis

Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged in the randomized CLL clinical study. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels, and the use of allopurinol during the first one to two weeks of TREANDA therapy in patients at high risk.

5.5 Skin Reactions

A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents, so the precise relationship to TREANDA is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, TREANDA should be withheld or discontinued.

5.6 Use in Pregnancy

TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. *[See Use in Specific Populations (8.1)]*

6 ADVERSE REACTIONS

The data described below reflect exposure to TREANDA in 153 patients. TREANDA was studied in an active-controlled trial. The population was 45-

77 years of age, 63% male, 100% white, and had treatment naïve CLL. All patients started the study at a dose of 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 every 28 days. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The following serious adverse reactions have been associated with TREANDA in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression *[See Warnings and Precautions (5.1)]*
- Infections *[See Warnings and Precautions (5.2)]*
- Infusion Reactions and Anaphylaxis *[See Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[See Warnings and Precautions (5.4)]*
- Skin Reactions *[See Warnings and Precautions (5.5)]*

Adverse reactions were reported according to NCI CTC v.2.0. In the randomized CLL clinical study, hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%). Non-hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with TREANDA in the randomized CLL clinical study and none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

The most frequent adverse reactions leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%) and pyrexia (1%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Table 1: Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	TREANDA (N=153)		Chlorambucil (N=143)	
System organ class Preferred term	All Grades	Grade 3/4	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction	**136 (89)**	**88 (58)**	**113 (79)**	**44 (31)**
Blood and lymphatic system disorders				
Neutropenia	43 (28)	36 (24)	20 (14)	13 (9)
Thrombocytopenia	35 (23)	20 (13)	28 (20)	11 (8)
Anemia	29 (19)	4 (3)	16 (11)	0
Leukopenia	28 (18)	23 (15)	4 (3)	2 (1)
Lymphopenia	10 (7)	10 (7)	0	0
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

Table 2: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study

	TREANDA N=150		Chlorambucil N=141	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

In the randomized CLL clinical study, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that significant deterioration does not occur.

7 DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between TREANDA and other drugs have been conducted.

Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

The role of active transport systems in bendamustine distribution has not been fully evaluated. *In vitro* data suggest that P-glycoprotein, breast cancer resistance protein (BCRP), and/or other efflux transporters may have a role in bendamustine transport.

Based on *in vitro* data, bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See Warnings and Precautions (5.6)]*

TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine from 210 mg/m^2 (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities) and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m^2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m^2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m^2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external [effect on tail, head, and herniation of external organs (exomphalos)] and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TREANDA in pediatric patients have not been established.

8.5 Geriatric Use

In the randomized CLL clinical study, 153 patients received TREANDA. The overall response rate for patients younger than 65 years of age was 70% (n=82) for TREANDA and 30% (n = 69) for chlorambucil. The overall response rate for patients 65 years or older was 47% (n=71) for TREANDA and 22% (n = 79) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the TREANDA group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the TREANDA group and 8 months in the chlorambucil group. The overall incidence of adverse reactions was 87% in patients < 65 years and 92 % in patients ≥ 65 years. There were no clinically significant differences in the adverse reaction profile.

8.6 Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild or moderate renal impairment. TREANDA should not be used in patients with CrCL < 40 mL/min. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild hepatic impairment. TREANDA should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. *[See Clinical Pharmacology (12.3)]*

8.8 Effect of Gender

In the randomized CLL clinical study, the overall response rate (ORR) for men (n=97) and women (n=56) in the TREANDA group was 60% and 57%, respectively. The ORR for men (n=90) and women (n=58) in the chlorambucil group was 24% and 28%, respectively. In this study, the median progression-free survival for men was 19 months in the TREANDA treatment group and 6 months in the chlorambucil treatment group. For women, the median progression-free survival was 13 months in the TREANDA treatment group and 8 months in the chlorambucil treatment group. No clinically significant differences between genders were seen in the overall incidences of adverse reactions.

10 OVERDOSAGE

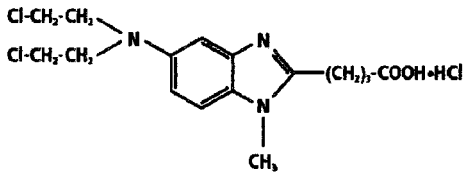
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

No specific antidote for TREANDA overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

11 DESCRIPTION

TREANDA contains bendamustine hydrochloride, an alkylating drug, as the active ingredient. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



TREANDA (bendamustine hydrochloride) for Injection is intended for intravenous infusion only after reconstitution with 20 mL of Sterile Water for Injection, USP and after further dilution with 0.9% Sodium Chloride Injection USP. It is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial. Each vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 - 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bendamustine is a bifunctional mechlorethamine derivative. Mechlorethamine and its derivatives dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

Bendamustine is active against both quiescent and dividing cells.

12.3 Pharmacokinetics

Absorption

Following a single IV dose of bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution

In vitro, the binding of bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 µg/mL. Data suggest that bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL indicating that bendamustine distributes freely in human red blood cells. In humans, the mean steady state volume of distribution (V_{ss}) was approximately 25 L.

Metabolism

In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. *In vitro*, studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine.

In vitro studies using human liver microsomes indicate that bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes.

Elimination

No mass balance study has been undertaken in humans. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m^2 bendamustine IV over 1-hour the intermediate $t_{½}$ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination $t_{½}$ of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle.

Renal Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. *[See Use in Specific Populations (8.6)]*

Hepatic Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5-10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. *[See Use in Specific Populations (8.7)]*

Effect of Age

Bendamustine exposure (as measured by AUC and C_{max}) has been studied in patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and Cmax) were not significantly different between patients less than or greater than/equal to 65 years of age. *[See Use in Specific Populations (8.4, 8.5)]*

Effect of Gender

The pharmacokinetics of bendamustine were similar in male and female patients. *[See Use in Specific Populations (8.8)]*

Effect of Race

The effect of race on the safety, and/or efficacy of TREANDA has not been established. Based on a cross-study comparison, Japanese subjects (n = 6) had on average exposures that were 40% higher than non-Japanese subjects receiving the same dose. The significance of this difference on the safety and efficacy of TREANDA in Japanese subjects has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bendamustine was carcinogenic in mice. After intraperitoneal injections at 37.5 mg/m^2/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m^2/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m^2/day (62.5 mg/kg/day, the only dose tested) for four days induced mammary carcinomas and pulmonary adenomas.

Bendamustine is a mutagen and clastogen. In a reverse bacterial mutation assay (Ames assay), bendamustine was shown to increase revertant frequency in the absence and presence of metabolic activation. Bendamustine was clastogenic in human lymphocytes *in vitro*, and in rat bone marrow cells *in vivo* (increase in micronucleated polychromatic erythrocytes) from 37.5 mg/m^2, the lowest dose tested.

Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.

14 CLINICAL STUDIES

The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the TREANDA and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7x10^9/L vs. 65.1x10^9/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immunophenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/m^2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL[1].

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for TREANDA compared to chlorambucil (see Table 3). Survival data are not mature.

Table 3: Efficacy Data

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR)†	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

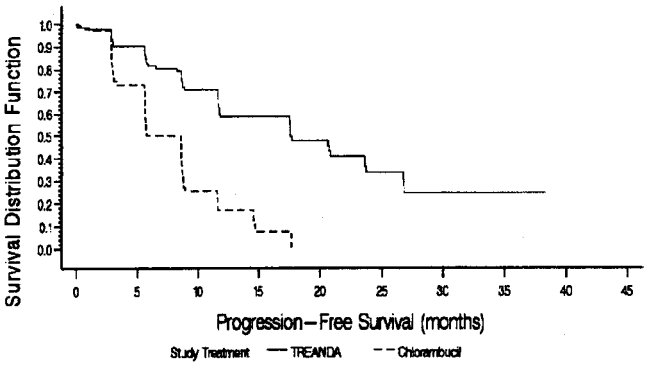
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

†† PFS was defined as time from randomization to progression or death from any cause.

Kaplan-Meier estimates of progression-free survival comparing TREANDA with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



15 REFERENCES

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2. Preventing occupational exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

3. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

4. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.

5. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published[2-5]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

16.2 How Supplied

TREANDA (bendamustine hydrochloride) for Injection is supplied in individual cartons of 20 mL amber single-use vials containing 100 mg of bendamustine hydrochloride as a white to off-white lyophilized powder.

NDC 63459-391-20 TREANDA (bendamustine hydrochloride) for Injection, 100 mg/vial

16.3 Storage

TREANDA may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION

- Allergic (Hypersensitivity) Reactions
  Patients should be informed of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion.

- Myelosuppression
  Patients should be informed of the likelihood that TREANDA will cause a decrease in white blood cells, platelets, and red blood cells. They will need frequent monitoring of these parameters. They should be instructed to report shortness of breath, significant fatigue, bleeding, fever, or other signs of infection.

- Pregnancy and Nursing
  TREANDA can cause fetal harm. Women should be advised to avoid becoming pregnant throughout treatment and for 3 months after TREANDA therapy has stopped. Men receiving TREANDA should use reliable contraception for the same time period. Advise patients to report pregnancy immediately. Advise patients to avoid nursing while receiving TREANDA.

- Fatigue
  Advise patients that TREANDA may cause tiredness and to avoid driving any vehicle or operating any dangerous tools or machinery if they experience this side effect.

- Nausea and Vomiting
  Advise patients that TREANDA may cause nausea and/or vomiting. Patients should report nausea and vomiting so that symptomatic treatment may be provided.

- Diarrhea
  Advise patients that TREANDA may cause diarrhea. Patients should report diarrhea to the physician so that symptomatic treatment may be provided.

- Rash
  Advise patients that a mild rash or itching may occur during treatment with TREANDA. Advise patients to immediately report severe or worsening rash or itching.

Cephalon Cephalon Oncology

Manufactured by:
Pharmachemie B.V.
The Netherlands

Manufactured for:
Cephalon, Inc.
Frazer, PA 19355

Label Code: PI-40014-00

資料３－③　ダビガトラン（dabigatran）

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of dabigatran etexilate (as mesilate)
Excipients: Each hard capsule contains 2 micrograms sunset yellow (E110)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Imprinted capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R75".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

4.2 Posology and method of administration

Prevention of Venous Thromboembolism (VTE) in patients following elective knee replacement surgery:

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Prevention of Venous Thromboembolism (VTE) in patients following elective hip replacement surgery:

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Special patient populations:

Renal impairment:

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated (see section 4.3).

In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4 and 5.1).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Elderly:

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4 and 5.1).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Hepatic impairment:

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. Therefore the use of Pradaxa is not recommended in this population (see sections 4.4 and 5.2). ALT should be measured as part of the standard pre-operative evaluation (see section 4.4).

Weight:

There is very limited clinical experience in patients with a body weight < 50 kg or > 110 kg at the recommended posology. Given the available clinical and kinetic data no adjustment is necessary (see section 5.2) but close clinical surveillance is recommended (see section 4.4).

Post-surgical patients with an increased risk for bleeding:

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), should be treated with caution (see sections 4.4 and 5.1).

Children and adolescents:

There is no experience in children and adolescents.
Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with Amiodarone:

Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section 4.5).

Switching from Pradaxa treatment to parenteral anticoagulant:

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (see section 4.5).

Switching from parenteral anticoagulants treatment to Pradaxa:

No data are available, therefore it is not recommended to start the administration of Pradaxa before the next scheduled dose of the parenteral anticoagulant would have been due (see section 4.5).

Pradaxa should be swallowed as a whole with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with quinidine (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment:

Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation.

Haemorrhagic risk:

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially in the following situations that may increase the hemorrhagic risk: diseases associated with an increased risk of bleeding, such as congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent biopsy or major trauma, recent intracranial haemorrhage or brain, spinal or ophthalmic surgery, bacterial endocarditis.

Patients with moderate renal impairment have an increased exposure to dabigatran. Limited data is available in patients < 50 kg and the elderly (see sections 4.2 and 5.2). In these situations, Pradaxa should be used with caution and a close clinical surveillance (looking for signs of bleeding or anemia) is required throughout the treatment period (see section 4.2).

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section 4.9).

Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section 4.5).

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events:

There are limited efficacy and safety data for dabigatran available in these patients and therefore they should be treated with caution.

Spinal anaesthesia/epidural anaesthesia/lumbar puncture:

In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of dabigatran and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with postoperative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Therefore the use of Pradaxa is not recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters.

Administration of the first dose of Pradaxa should occur a minimum of two hours after the catheter is removed. These patients require frequent observation for neurological signs and symptoms.

Hip fracture surgery:

There is no data on the use of Pradaxa in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Colorants:

Pradaxa hard capsules contain the colorant sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents:

The following treatments are not recommended concomitantly with Pradaxa: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see sections 4.2 and 4.4).

Interactions linked to dabigatran etexilate and dabigatran metabolic profile:

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

NSAIDs: When Pradaxa was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see section 4.4).

Transporter interactions:

Amiodarone: Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and dabigatran etexilate a substrate of this transporter. When Pradaxa was coadministered with amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section 4.2).

P- glycoprotein inhibitors:
Caution should be exercised with strong P- glycoprotein inhibitors like verapamil, clarithromycin, and others. The P- glycoprotein inhibitor quinidine is contraindicated (see section 4.3).

P- glycoprotein inducers:
Potent P- glycoprotein inducers such as rifampicin or St John's wort (Hypericum perforatum), may reduce the systemic exposure of dabigatran. Caution is advised when co-administering these medicinal products.

Digoxin: In a study performed with 24 healthy subjects, when Pradaxa was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed.

Gastric pH:

Pantoprazole: When Pradaxa was coadministered with pantoprazole, a decrease in the dabigatran area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with Pradaxa in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate data from the use of Pradaxa in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate.
Pradaxa should not be used during pregnancy unless clearly necessary.

Lactation:

There are no clinical data of the effect of dabigatran on infants during breast feeding.
Lactation should be discontinued during treatment with Pradaxa.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

A total of 10.084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5419 were treated with 150 mg or 220 mg daily of Pradaxa, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

The table 1 shows the number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

Table 1 Bleeding events broken down to major and any bleeding in the pivotal hip and knee study.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Treated	1866(100.0)	1825(100.0)	1848(100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258(13.8)	251(13.8)	247(13.4)

Table 2 shows the adverse reactions ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (< 1/10,000).

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Number of patients treated	2737(100)	2682(100)	3108(100)
Blood and lymphatic system disorders			
	Common		
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
	Uncommon		
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Vascular disorders			
	Common		
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Wound haemorhhage	35 (1.3)	28 (1.0)	31 (1.0)
	Uncommon		
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Respiratory and thoracic system disorders			
	Uncommon		
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastrointestinal disorders			
	Common		
Gastrointestinal haemorrhage	33 (1.2)	17 (0.6)	20 (0.6)
	Uncommon		
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Haemorrhoidal haemorrhage	4 (0.2)	8 (0.3)	2 (0.1)
Hepatobiliary disorders			
	Uncommon		
Alaninine aminotransferase increased	18 (0.7)	7 (0.3)	28 (0.9)
Aspartate aminotransferase increased	9 (0.3)	5 (0.2)	15 (0.5)
Hepatic function abnormal/ Liver function Test abnormal	6 (0.2)	10 (0.4)	7 (0.2)
Hepatic enzyme increased	4 (0.2)	5 (0.2)	11 (0.4)

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Hyperbilirubinaemia	4 (0.1)	3 (0.1)	4 (0.1)
Transaminases increased	0 (0.0)	2 (0.1)	1 (0.0)
Skin and subcutaneous tissue disorder			
	Common		
Skin haemorrhage	45 (1.6)	57 (2.1)	61 (2.0)
Musculoskeletal and connective tissue and bone disorders			
	Uncommon		
Haemarthrosis	9 (0.3)	7 (0.3)	17 (0.6)
Renal and urinary disorders			
	Common		
Haematuria	38 (1.4)	33 (1.4)	25 (0.8)
General disorders and administration site conditions			
	Uncommon		
Injection site haemorrhage	21 (0.8)	19 (0.7)	27 (0.9)
Bloody discharge	2 (0.1)	6 (0.2)	6 (0.2)
Catheter site haemorrhage	2 (0.1)	1 (0.0)	7 (0.2)
Investigations			
	Common		
Haemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)
	Uncommon		
Haematocrit decreased	0 (0.0)	6 (0.2)	4 (0.1)
Injury, poisoning and procedural complications			
	Common		
Wound secretion	130 (4.8)	130 (4.9)	93 (3.0)
Anaemia postoperative	99 (3.6)	87 (3.2)	120 (3.7)
Post procedural haematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post procedural haemorrhage	37 (1.4)	54 (2.0)	56 (1.8)
Post procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Surgical and medial procedures			
	Uncommon		
Post procedural drainage	11 (0.4)	13 (0.5)	16 (0.5)
Wound drainage	1 (0.0)	4 (0.2)	2 (0.1)

Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase 3 studies as presented in table 3.

Table 3: ALT findings the following laboratory chemistry

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Total rates of Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

4.9 Overdose

There is no antidote to dabigatran. Doses of dabigatran etexilate beyond those recommended, expose the patient to increased risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

Dabigatran can be dialysed; there is no clinical experience to demonstrate the utility of this approach in clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine inhibitors, ATC code: B01AE07

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.
Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and *ex-vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies.

Steady state (after day 3) dabigatran peak plasma concentration, measured 2 - 4 hours after 220 mg dabigatran etexilate administration, is expected to be around 270 ng/ml, with an expected range of 80 - 460 ng/ml. The dabigatran trough concentration, measured at the end of the dosing interval (24 hours after the last 220 mg dabigatran dose), is expected to be around 40 ng/ml, with expected range of 10-90 ng/ml.

Ethnic origin:

More than 99% of efficacy and safety data were generated in Caucasians.

Clinical trials in Venous Thromboembolism (VTE) prophylaxis following major joint replacement surgery:

In 2 large randomized, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received Pradaxa 75 mg or 110 mg within 1-4 hours of surgery followed by 150 mg or 220 mg daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.
In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

Composite of total VTE (including PE, proximal and distal DVT, whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic

detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.
Results of both studies showed that the antithrombotic effect of Pradaxa 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of Major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 4). Better results were seen with the 220mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 4)."

The clinical studies have been conducted in a patient population with a mean age > 65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5539 patients treated), 51 % suffered from concomitant hypertension, 9 % from concomitant diabetes, 9 % from concomitant coronary artery disease and 20 % had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 4.

Data for the total VTE and all cause mortality endpoint are shown in table 5.

Data for adjudicated major bleeding endpoints are shown in tables 6 below.

Table 4: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopeadic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Table 5: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	880	874	897
Incidences (%)	53 (6.0)	75 (8.6)	60 (6.7)
Risk ratio over	0.9	1.28	

enoxaparin			
95% CI	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL (knee)			
N	503	526	512
Incidences (%)	183 (36.4)	213 (40.5)	193 (37.7)
Risk ratio over enoxaparin	0.97	1.07	
95% CI	(0.82, 1.13)	(0.92, 1.25)	

Table 6: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.8)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

5.2 Pharmacokinetic properties

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of Pradaxa was approximately 6.5 %.
After oral administration of Pradaxa in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with Cmax attained within 0.5 and 2.0 hours post administration.

Absorption:

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.
Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

Distribution:

Low (34-35 %) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigtran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.
Cmax and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12 - 14 hours in healthy volunteers and 14 – 17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose.

Metabolism and elimination:

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabeled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

Special populations:

Renal insufficiency:
The exposure (AUC) of dabigatran after the oral administration of Pradaxa is approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 – 50 ml/min) than in those without renal insufficiency.

In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2, 4.3 and 4.4).

Elderly patients:
Specific pharmacokinetic studies with elderly subjects showed an increase of 40 to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects. Population-based pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran after repeated doses in patients (up to 88 years). The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance (see sections 4.2 and 4.4).

Hepatic insufficiency:
No change in dabigatran exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see sections 4.2 and 4.4).

Body weight:
Population pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight (see section 4.2 and 4.4).

Gender:
Active substance exposure in female patients is about 40 % to 50 % higher than in male patients and no dose adjustment is recommended.

Ethnic origin:
The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. No pharmacokinetic data in black patients are available.

Pharmacokinetic interactions:
In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any

interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-glycoprotein transporter interaction) and diclofenac (CYP2C9).
Dabigatran exposure in healthy subjects was increased by 60 % in the presence of amiodarone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeat-dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5 to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

Carcinogenicity studies have not yet been completed with dabigatran.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
- Tartaric acid
- Acacia
- Hypromellose
- Dimeticone 350
- Talc
- Hydroxypropylcellulose

Capsule shell
- Carrageenan
- Potassium Chloride
- Titanium Dioxide
- Indigo Carmine (E132)
- Sunset Yellow (E110)
- Hypromellose
- Water purified

Black printing ink

- Shellac
- N-Butyl alcohol
- Isopropyl alcohol
- Industrial methylated spirit
- Iron oxide black (E172)
- Purified water
- Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 2 years

Once the bottle is opened, the product must be used within 30 days

6.4 Special precautions for storage

Blister:

Store in the original package in order to protect from moisture

Bottle:

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, or 60 x 1 hard capsules) in coated aluminium perforated unit dose blisters. The aluminium unit dose blister is coated with polyvinylchloridevinylacetate copolymers acrylate (PVACAC) and polyvinylchlorid (PVC)).

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When taking Pradaxa capsules out of the blister pack, the following instructions should be followed:

- The hard capsules should be taken out of the blister card by peeling off the backing foil.
- The hard capsules should not be pushed through the blister foil.
- The blister foil should only be peeled off, when a hard capsule is required.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 110 mg of dabigatran etexilate (as mesilate)
Excipients: Each hard capsule contains 3 micrograms sunset yellow (E110)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Imprinted capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R110".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

4.2 Posology and method of administration

Prevention of Venous Thromboembolism (VTE) in patients following elective knee replacement surgery:

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Prevention of Venous Thromboembolism (VTE) in patients following elective hip replacement surgery:

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Special patient populations:

Renal impairment:

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated (see section 4.3).

In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4 and 5.1).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Elderly:

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4 and 5.1).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Hepatic impairment:

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. Therefore the use of Pradaxa is not recommended in this population (see sections 4.4 and 5.2). ALT should be measured as part of the standard pre-operative evaluation (see section 4.4).

Weight:

There is very limited clinical experience in patients with a body weight < 50 kg or > 110 kg at the recommended posology. Given the available clinical and kinetic data no adjustment is necessary (see section 5.2) but close clinical surveillance is recommended (see section 4.4).

Post-surgical patients with an increased risk for bleeding:

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), should be treated with caution (see sections 4.4 and 5.1).

Children and adolescents:

There is no experience in children and adolescents.
Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with Amiodarone:

Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section 4.5).

Switching from Pradaxa treatment to parenteral anticoagulant:

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (see section 4.5).

Switching from parenteral anticoagulants treatment to Pradaxa:

No data are available, therefore it is not recommended to start the administration of Pradaxa before the next scheduled dose of the parenteral anticoagulant would have been due (see section 4.5).

Pradaxa should be swallowed as a whole with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with quinidine (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment:

Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation.

Haemorrhagic risk:

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially in the following situations that may increase the hemorrhagic risk: diseases associated with an increased risk of bleeding, such as congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, active ulcerative gastrointestinal disease, recent biopsy or major trauma, recent intracranial haemorrhage or brain, spinal or ophthalmic surgery, bacterial endocarditis.

Patients with moderate renal impairment have an increased exposure to dabigatran. Limited data is available in patients < 50 kg and the elderly (see sections 4.2 and 5.2). In these situations, Pradaxa should be used with caution and a close clinical surveillance (looking for signs of bleeding or anemia) is required throughout the treatment period (see section 4.2).

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section 4.9).

Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section 4.5).

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events:

There are limited efficacy and safety data for dabigatran available in these patients and therefore they should be treated with caution.

Spinal anaesthesia/epidural anaesthesia/lumbar puncture:

In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of dabigatran and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with postoperative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Therefore the use of Pradaxa is not recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters.

Administration of the first dose of Pradaxa should occur a minimum of two hours after the catheter is removed. These patients require frequent observation for neurological signs and symptoms.

Hip fracture surgery:

There is no data on the use of Pradaxa in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

Colorants:

Pradaxa hard capsules contain the colorant sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents:

The following treatments are not recommended concomitantly with Pradaxa: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see sections 4.2 and 4.4).

Interactions linked to dabigatran etexilate and dabigatran metabolic profile:

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

NSAIDs: When Pradaxa was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see section 4.4).

Transporter interactions:

Amiodarone: Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and dabigatran etexilate a substrate of this transporter. When Pradaxa was coadministered with amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dosing should be reduced to 150 mg Pradaxa daily in patients who received concomitantly dabigatran etexilate and amiodarone (see section 4.2).

P- glycoprotein inhibitors:
Caution should be exercised with strong P- glycoprotein inhibitors like verapamil, clarithromycin, and others. The P- glycoprotein inhibitor quinidine is contraindicated (see section 4.3).

P- glycoprotein inducers:
Potent P- glycoprotein inducers such as rifampicin or St John's wort (Hypericum perforatum), may reduce the systemic exposure of dabigatran. Caution is advised when co-administering these medicinal products.

Digoxin: In a study performed with 24 healthy subjects, when Pradaxa was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed.

Gastric pH:

Pantoprazole: When Pradaxa was coadministered with pantoprazole, a decrease in the dabigatran area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with Pradaxa in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate data from the use of Pradaxa in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate.
Pradaxa should not be used during pregnancy unless clearly necessary.

Lactation:

There are no clinical data of the effect of dabigatran on infants during breast feeding.
Lactation should be discontinued during treatment with Pradaxa.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

A total of 10.084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5419 were treated with 150 mg or 220 mg daily of Pradaxa, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

The table 1 shows the number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

Table 1 Bleeding events broken down to major and any bleeding in the pivotal hip and knee study.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Treated	1866(100.0)	1825(100.0)	1848(100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258(13.8)	251(13.8)	247(13.4)

Table 2 shows the adverse reactions ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (< 1/10,000).

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Number of patients treated	2737(100)	2682(100)	3108(100)
Blood and lymphatic system disorders			
	Common		
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
	Uncommon		
Thrombocytopenia	5 (0.2)	2 (0.1)	5 (0.2)
Vascular disorders			
	Common		
Haematoma	38 (1.4)	37 (1.4)	55 (1.8)
Traumatic haematoma	37 (1.4)	41 (1.5)	51 (1.6)
Wound haemorhhage	35 (1.3)	28 (1.0)	31 (1.0)
	Uncommon		
Haemorrhage	5 (0.2)	18 (0.7)	21 (0.7)
Respiratory and thoracic system disorders			
	Uncommon		
Epistaxis	19 (0.7)	15 (0.6)	13 (0.4)
Gastrointestinal disorders			
	Common		
Gastrointestinal haemorrhage	33 (1.2)	17 (0.6)	20 (0.6)
	Uncommon		
Rectal haemorrhage	12 (0.4)	15 (0.6)	5 (0.2)
Haemorrhoidal haemorrhage	4 (0.2)	8 (0.3)	2 (0.1)
Hepatobiliary disorders			
	Uncommon		
Alaninine aminotransferase increased	18 (0.7)	7 (0.3)	28 (0.9)
Aspartate aminotransferase increased	9 (0.3)	5 (0.2)	15 (0.5)
Hepatic function abnormal/ Liver function Test abnormal	6 (0.2)	10 (0.4)	7 (0.2)
Hepatic enzyme increased	4 (0.2)	5 (0.2)	11 (0.4)

SOC / Preferred Term.	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Hyperbilirubinaemia	4 (0.1)	3 (0.1)	4 (0.1)
Transaminases increased	0 (0.0)	2 (0.1)	1 (0.0)
Skin and subcutaneous tissue disorder			
	Common		
Skin haemorrhage	45 (1.6)	57 (2.1)	61 (2.0)
Musculoskeletal and connective tissue and bone disorders			
	Uncommon		
Haemarthrosis	9 (0.3)	7 (0.3)	17 (0.6)
Renal and urinary disorders			
	Common		
Haematuria	38 (1.4)	33 (1.4)	25 (0.8)
General disorders and administration site conditions			
	Uncommon		
Injection site haemorrhage	21 (0.8)	19 (0.7)	27 (0.9)
Bloody discharge	2 (0.1)	6 (0.2)	6 (0.2)
Catheter site haemorrhage	2 (0.1)	1 (0.0)	7 (0.2)
Investigations			
	Common		
Haemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)
	Uncommon		
Haematocrit decreased	0 (0.0)	6 (0.2)	4 (0.1)
Injury, poisoning and procedural complications			
	Common		
Wound secretion	130 (4.8)	130 (4.9)	93 (3.0)
Anaemia postoperative	99 (3.6)	87 (3.2)	120 (3.7)
Post procedural haematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post procedural haemorrhage	37 (1.4)	54 (2.0)	56 (1.8)
Post procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Surgical and medial procedures			
	Uncommon		
Post procedural drainage	11 (0.4)	13 (0.5)	16 (0.5)
Wound drainage	1 (0.0)	4 (0.2)	2 (0.1)

Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase 3 studies as presented in table 3.

Table 3: ALT findings the following laboratory chemistry

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Total rates of Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

4.9 Overdose

There is no antidote to dabigatran. Doses of dabigatran etexilate beyond those recommended, expose the patient to increased risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

Dabigatran can be dialysed; there is no clinical experience to demonstrate the utility of this approach in clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine inhibitors, ATC code: B01AE07

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.
Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and *ex-vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies.

Steady state (after day 3) dabigatran peak plasma concentration, measured 2 - 4 hours after 220 mg dabigatran etexilate administration, is expected to be around 270 ng/ml, with an expected range of 80 - 460 ng/ml. The dabigatran trough concentration, measured at the end of the dosing interval (24 hours after the last 220 mg dabigatran dose), is expected to be around 40 ng/ml, with expected range of 10-90 ng/ml.

Ethnic origin:

More than 99% of efficacy and safety data were generated in Caucasians.

Clinical trials in Venous Thromboembolism (VTE) prophylaxis following major joint replacement surgery:

In 2 large randomized, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received Pradaxa 75 mg or 110 mg within 1-4 hours of surgery followed by 150 mg or 220 mg daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.
In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

Composite of total VTE (including PE, proximal and distal DVT, whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic

detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.
Results of both studies showed that the antithrombotic effect of Pradaxa 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of Major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 4). Better results were seen with the 220mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 4)."

The clinical studies have been conducted in a patient population with a mean age > 65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5539 patients treated), 51 % suffered from concomitant hypertension, 9 % from concomitant diabetes, 9 % from concomitant coronary artery disease and 20 % had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 4.

Data for the total VTE and all cause mortality endpoint are shown in table 5.

Data for adjudicated major bleeding endpoints are shown in tables 6 below.

Table 4: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopeadic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Table 5: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	880	874	897
Incidences (%)	53 (6.0)	75 (8.6)	60 (6.7)
Risk ratio over	0.9	1.28	

enoxaparin			
95% CI	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL (knee)			
N	503	526	512
Incidences (%)	183 (36.4)	213 (40.5)	193 (37.7)
Risk ratio over enoxaparin	0.97	1.07	
95% CI	(0.82, 1.13)	(0.92, 1.25)	

Table 6: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.8)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

5.2 Pharmacokinetic properties

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of Pradaxa was approximately 6.5 %.
After oral administration of Pradaxa in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with Cmax attained within 0.5 and 2.0 hours post administration.

Absorption:

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.
Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

Distribution:

Low (34-35 %) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigtran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.
Cmax and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12 - 14 hours in healthy volunteers and 14 – 17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose.

Metabolism and elimination:

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabeled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

Special populations:

Renal insufficiency:
The exposure (AUC) of dabigatran after the oral administration of Pradaxa is approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 – 50 ml/min) than in those without renal insufficiency.

In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2, 4.3 and 4.4).

Elderly patients:
Specific pharmacokinetic studies with elderly subjects showed an increase of 40 to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects. Population-based pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran after repeated doses in patients (up to 88 years). The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance (see sections 4.2 and 4.4).

Hepatic insufficiency:
No change in dabigatran exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see sections 4.2 and 4.4).

Body weight:
Population pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight (see section 4.2 and 4.4).

Gender:
Active substance exposure in female patients is about 40 % to 50 % higher than in male patients and no dose adjustment is recommended.

Ethnic origin:
The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. No pharmacokinetic data in black patients are available.

Pharmacokinetic interactions:
In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any

interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-glycoprotein transporter interaction) and diclofenac (CYP2C9).
Dabigatran exposure in healthy subjects was increased by 60 % in the presence of amiodarone.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeat-dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5 to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

Carcinogenicity studies have not yet been completed with dabigatran.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

- Tartaric acid
- Acacia
- Hypromellose
- Dimeticone 350
- Talc
- Hydroxypropylcellulose

Capsule shell

- Carrageenan
- Potassium Chloride
- Titanium Dioxide
- Indigo Carmine (E132)
- Sunset Yellow (E110)
- Hypromellose
- Water purified

Black printing ink

- Shellac
- N-Butyl alcohol
- Isopropyl alcohol
- Industrial methylated spirit
- Iron oxide black (E172)
- Purified water
- Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 2 years

Once the bottle is opened, the product must be used within 30 days

6.4 Special precautions for storage

Blister:

Store in the original package in order to protect from moisture

Bottle:

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, or 60 x 1 hard capsules) in coated aluminium perforated unit dose blisters. The aluminium unit dose blister is coated with polyvinylchloridevinylacetate copolymers acrylate (PVACAC) and polyvinylchlorid (PVC)).

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When taking Pradaxa capsules out of the blister pack, the following instructions should be followed:

- The hard capsules should be taken out of the blister card by peeling off the backing foil.
- The hard capsules should not be pushed through the blister foil.
- The blister foil should only be peeled off, when a hard capsule is required.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 4.0 dated 30 July 2007 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 01 dated 11 January 2007 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg dabigatran etexilate (as mesilate)

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM YYYY

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 110 mg dabigatran etexilate (as mesilate)

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsules
[redacted]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM YYYY

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP MM YYYY

4. BATCH NUMBER

Lot

5. OTHER

Peel back

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP MM YYYY

4. BATCH NUMBER

Lot

5. OTHER

Peel back

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

FOLDING BOX AND LABEL FOR BOTTLE for 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg dabigatran etexilate (as mesilate)

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110) (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM YYYY
Once opened, the product must be used within 30 days

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed. Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 75 mg [redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.

FOLDING BOX AND LABEL FOR BOTTLE for 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 110 mg dabigatran etexilate (as mesilate)

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110) (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM YYYY
Once opened, the product must be used within 30 days

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed. Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg [redacted]

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pradaxa 75 mg hard capsules
Pradaxa 110 mg hard capsules
dabigatran etexilate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PRADAXA IS AND WHAT IT IS USED FOR

What is Pradaxa:

Pradaxa is a medicine which is used to prevent the formation of blood clots. It works by blocking a substance in the body which is involved in blood clot formation.

What Pradaxa is used for:

Pradaxa is used to prevent the formation of blood clots in the veins after knee or hip replacement surgery.

2. BEFORE YOU TAKE PRADAXA

Do NOT take Pradaxa

- if you are allergic to dabigatran etexilate, dabigatran or any of the other ingredients of Pradaxa.
- if you have severely reduced kidney function.
- if you are currently bleeding
- if you have a disease in an organ of the body that increases the risk of serious bleeding.
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you have a severely reduced liver function or liver disease which could possibly cause death.
- if you are taking quinidine, a medicine to treat abnormal heart beats.

Take special care with Pradaxa

Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have a liver disease that is associated with changes in the blood tests, the use of Pradaxa is not recommended.

- if you have an increased bleeding risk, as could be the case in the following situations:
  - if you have had a surgical tissue removal (biopsy) in the past month.
  - if you have had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if you are receiving treatments which could increase the risk of bleeding.
  - if you are taking anti-inflammatory medicines.
  - if you are suffering from an infection of the heart (bacterial endocarditis).
  - if you have a moderately impaired kidney function.
  - Pradaxa should not be used in children.

- if you have a tube (catheters) inserted into the back:
  A tube can be inserted into your back e.g. for anesthesia or pain relief during or after surgery. If you are administered Pradaxa after removal of a catheter your doctor will examine you regularly.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. For instance:

- Blood thinners (e.g. warfarin, heparin)
- Non-steroidal anti-inflammatory medicines
- St. John´s wort, rifampicin, verapamil, clarithromycin
- Amiodarone
  If you are taking amiodarone-containing medicines you should be treated with a reduced dose of 150 mg Pradaxa

Taking Pradaxa with food and drink

Pradaxa can be taken with or without food.

Pregnancy and breast-feeding

The effects of Pradaxa on pregnancy and the unborn child are not known. You should not take Pradaxa if you are pregnant unless your doctor advises you that it is safe to do so. If you are a woman of child-bearing age, you should avoid becoming pregnant while you are taking Pradaxa.

You should not breast-feed while you are taking Pradaxa.

Driving and using machines

The effect of Pradaxa on the ability to drive and use machines is not known. Your doctor will tell you when you can start to drive.

Important information about some of the ingredients of Pradaxa

Pradaxa hard capsules contain a colorant with the name sunset yellow, which may cause allergic reactions.

3. HOW TO TAKE PRADAXA

When taking Pradaxa capsules out of the blister pack, please observe the following instructions

- take the capsules by peeling off the backing foil of the blister card.
- do not push the capsules through the blister foil.
- do not peel off the blister foil until a capsule is required.

When taking Pradaxa capsules out of the bottle, please observe the following instructions

- push and turn for opening

The generally recommended dose of Pradaxa is 220 mg once a day (taken as 2 capsules of 110 mg).

If your kidney function is decreased by more than half or if you are 75 years of age or older, the recommended dose is 150 mg once a day (taken as 2 capsules of 75 mg).

After knee replacement surgery

You should start treatment with Pradaxa within 1 – 4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 10 days.

After hip replacement

You should start treatment with Pradaxa within 1 – 4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 28 - 35 days.

For both surgery types, treatment should not be started if there is bleeding from the site of operation. If the treatment cannot be started until the day after surgery, dosing should be started with 2 capsules once daily.

Always take Pradaxa exactly as your doctor has told you. You should check with your doctor if you are not sure. The capsule should be swallowed with some water. Do not chew the capsule.

Changing from treatment with Pradaxa to anticoagulant treatment given by injection
Do not start treatment with injectable anticoagulant medicines (for example, heparin) until 24 hours after the final dose of Pradaxa.

Changing from anticoagulant treatment given by injection to treatment with Pradaxa
Stop the treatment by injection and then start taking Pradaxa at the time you would have had the next injection.

If you take more Pradaxa than you should
If you take more Pradaxa than recommended, you may have an increased risk of bleeding. Your doctor can perform a blood test to assess the risk of bleeding.
Inform your doctor as soon as possible if you take more than the prescribed dose of Pradaxa. If bleeding occurs, surgical treatment or treatment with blood transfusions may be required.

If you forget to take Pradaxa
Continue with your remaining daily doses of Pradaxa at the same time of the next day.
Do not take a double dose to make up for missed individual doses.

If you stop taking Pradaxa
Do not stop taking Pradaxa without first consulting your doctor, since the risk of developing a blood clot in a vein could be higher if you stop treatment early.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pradaxa can cause side effects, although not in all patients.

As this medicine affects blood clotting, most side effects are related to signs such as bruising or bleeding.

The side effects are listed below, grouped by how likely they are to happen:

With Pradaxa the following common and uncommon side effects are known:

Common side effects (affects 1 to 10 users in 100):
- A fall in the number of red cells in the blood
- Haematoma formation
- Bleeding from an injury
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Wound secretion (liquid exuding from the surgical wound)
- Bruising occurring after an operation
- Bleeding occurring after an operation
- A fall in the number of red cells in the blood after an operation
- Bruising due to an injury
- Exudation of a small amount of liquid from the incision made for a surgical procedure
- Blood found in the urine on laboratory testing.

Uncommon side effects (affects 1 to 10 users in 1,000):
- Bleeding
- Bleeding into a joint
- A fall in the number of platelets in the blood
- Nose bleed
- Bleeding into the stomach or bowel
- Bleeding from piles
- Bleeding into the rectum
- Blood in the urine that stains the urine pink or red
- Bleeding under the skin
- Blood-stained discharge from the site of entry of a catheter into a vein
- Bleeding from the site of entry of a catheter into a vein
- Blood detected in the stools by a laboratory test
- A decrease in the proportion of red cells in the blood
- Bleeding from a surgical incision
- Unusual laboratory test results on liver function

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PRADAXA

Keep out of the reach and sight of children.

Do not use Pradaxa after the expiry date which is stated on the carton, blister or bottle. The expiry date refers to the last day of that month.

Blister: Store in the original package in order to protect from moisture.
Bottle: Once opened, the product must be used within 30 days. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pradaxa contains

The active substance is dabigatran, which is administered in the form of 75 mg or 110 mg dabigatran etexilate given as mesilate.

The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose

The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, sunset yellow, hypromellose and purified water

The black printing ink contains shellac, N-butyl alcohol, isopropyl alcohol, industrial methylated spirit, iron oxide black, purified water and propylene glycol

What Pradaxa looks like and contents of the pack

Pradaxa is a hard capsule.

Pradaxa 75 mg hard capsules have an opaque, light blue-coloured cap and an opaque, cream-coloured body. The Boehringer Ingelheim logo is printed on the cap and "R75" on the body of the capsule.

Pradaxa 110 mg hard capsules have an opaque, light blue-coloured cap and an opaque, cream-coloured body. The Boehringer Ingelheim logo is printed on the cap and "R110" on the body of the capsule.

Pradaxa 75 mg and 110 mg hard capsules are available in packs containing 10 x 1, 30 x 1, 60 x 1 capsules in aluminium perforated unit dose blisters.

Pradaxa 75 mg and 110 mg hard capsules are also available in polypropylene (plastic) bottles with 60 hard capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Binger Strasse 173

D-55216 Ingelheim am Rhein
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Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Lexiscan™ (regadenoson) injection for intravenous administration

Initial U.S. Approval: 2008

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

Lexiscan is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress. (1)

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

- The recommended dose of Lexiscan is 5 mL (0.4 mg regadenoson) by rapid intravenous injection; followed immediately by saline flush and radiopharmaceutical (2)

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

- Single-use vial: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL) (3)
- Single-use pre-filled syringe: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL) (3)

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

Do not administer Lexiscan to patients with:

- second or third degree AV block, or
- sinus node dysfunction

unless the patients have a functioning artificial pacemaker. (4)

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

- Fatal cardiac arrest, life threatening ventricular arrhythmias, or myocardial infarction may be induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan. (5.1)
- Sinoatrial (SA) and atrioventricular (AV) nodal block. Adenosine receptor agonists including Lexiscan can depress the SA and AV nodes and may cause first-, second- or third-degree AV block, or sinus bradycardia. (5.2)
- Hypotension. Adenosine receptor agonists including Lexiscan induce vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or hypovolemia. (5.3)
- Adenosine receptor agonists may induce bronchoconstriction and respiratory compromise in patients with COPD or asthma. Resuscitative measures should be available. (5.4)

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

The most common (incidence ≥ 5%) adverse reactions to Lexiscan are dyspnea, headache, flushing, chest discomfort, dizziness, angina pectoris, chest pain, and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. (1-800-727-7003) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Methylxanthines, e.g., caffeine and theophylline, may interfere with the activity of Lexiscan (7.1)
- Aminophylline may be used to attenuate severe and/or persistent adverse reactions to Lexiscan (7.1, 10)
- Dipyridamole may increase the activity of Lexiscan. When possible, withhold dipyridamole for at least two days prior to Lexiscan administration (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Lexiscan™ (regadenoson) injection is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.

2 DOSAGE AND ADMINISTRATION

The recommended intravenous dose of Lexiscan is 5 mL (0.4 mg regadenoson)

- Administer Lexiscan as a rapid (approximately 10 seconds) injection into a peripheral vein using a 22 gauge or larger catheter or needle.
- Administer a 5 mL saline flush immediately after the injection of Lexiscan.
- Administer the radionuclide myocardial perfusion imaging agent 10–20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as Lexiscan.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Lexiscan if it contains particulate matter or is discolored.

3 DOSAGE FORMS AND STRENGTHS

- Single-use vial: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL).
- Single-use pre-filled syringe: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL).

4 CONTRAINDICATIONS

Do not administer Lexiscan to patients with:

- second or third degree AV block, or
- sinus node dysfunction

unless these patients have a functioning artificial pacemaker [*see Warnings and Precautions* (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia

Fatal cardiac arrest, life threatening ventricular arrhythmias, and myocardial infarction may result from the ischemia induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan. If serious reactions to Lexiscan occur, consider the use of aminophylline, an adenosine antagonist, to shorten the duration of increased coronary blood flow induced by Lexiscan [*see Overdosage* (10)].

5.2 Sinoatrial and Atrioventricular Nodal Block

Adenosine receptor agonists including Lexiscan can depress the SA and AV nodes and may cause first-, second- or third-degree AV block, or sinus bradycardia. In clinical trials first degree AV block (PR prolongation > 220 msec) developed in 3% of patients within 2 hours of Lexiscan administration; transient second degree AV block with one dropped beat was observed in one patient receiving Lexiscan. All episodes of AV block were asymptomatic and did not require intervention.

5.3 Hypotension

Adenosine receptor agonists including Lexiscan induce arterial vasodilation and hypotension. Decreased systolic blood pressure (> 35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (> 25 mm Hg) was observed in 4% of patients within 45 min of Lexiscan administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.

5.4 Bronchoconstriction

Adenosine receptor agonists may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD) or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration [*see Overdosage* (10) *and Patient Counseling Information* (17.3)].

The incidence of bronchoconstriction (FEV_1 reduction > 15% from baseline) was assessed in two clinical studies. In a randomized, controlled study of 49 patients with moderate to severe COPD, the rate of bronchoconstriction was 12% and 6%, for the Lexiscan and placebo groups, respectively. In a randomized, controlled study of 48 patients with mild to moderate asthma who had previously been shown to have bronchoconstrictive reactions to adenosine monophosphate, the rate of bronchoconstriction was the same (4%) for both the Lexiscan and placebo groups. In both studies, dyspnea was reported as an adverse reaction in the Lexiscan group (61% for patients with COPD; 34% for patients with asthma) while no subjects in the placebo group experienced dyspnea.

6 ADVERSE REACTIONS

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

During clinical development, 1,651 subjects were exposed to Lexiscan, with most receiving 0.4 mg as a rapid (≤ 10 seconds) intravenous injection. Most of these subjects received Lexiscan in two clinical studies that enrolled patients who had no history of bronchospastic lung disease as well as no history of a cardiac conduction block of greater than first degree AV block, except for patients with functioning artificial pacemakers. In these studies

Table 2

Rhythm or Conduction Abnormalities* in Studies 1 and 2

	Lexiscan N / N evaluable (%)	Adenoscan N / N evaluable (%)
Rhythm or conduction abnormalities†	332/1275 (26%)	192/645 (30%)
Rhythm abnormalities	260/1275 (20%)	131/645 (20%)
PACs	86/1274 (7%)	57/645 (9%)
PVCs	179/1274 (14%)	79/645 (12%)
1st degree AV block (PR prolongation > 220 msec)	34/1209 (3%)	43/618 (7%)
2nd degree AV block	1/1209 (0.1%)	9/618 (1%)
AV conduction abnormalities (other than AV blocks)	1/1209 (0.1%)	0/618 (0%)
Ventricular conduction abnormalities	64/1152 (6%)	31/581 (5%)

* 12-lead ECGs were recorded before and for up to 2 hrs after dosing

† includes rhythm abnormalities (PACs, PVCs, atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular or ventricular arrhythmia) or conduction abnormalities, including AV block

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with Lexiscan.

7.1 Effects of Other Drugs on Lexiscan

- Methylxanthines (e.g., caffeine and theophylline) are non-specific adenosine receptor antagonists and may interfere with the vasodilation activity of Lexiscan [*see Clinical Pharmacology* (12.2) *and Patient Counseling Information* (17.1)]. Patients should avoid consumption of any products containing methylxanthines as well as any drugs containing theophylline for at least 12 hours before Lexiscan administration. Aminophylline may be used to attenuate severe or persistent adverse reactions to Lexiscan [*see Overdosage* (10)].
- In clinical studies, Lexiscan was administered to patients taking other cardioactive drugs (i.e., β-blockers, calcium channel blockers, ACE inhibitors, nitrates, cardiac glycosides, and angiotensin receptor blockers) without reported adverse reactions or apparent effects on efficacy.
- Dipyridamole may change the effects of Lexiscan. When possible, withhold dipyridamole for at least two days prior to Lexiscan administration.

7.2 Effect of Lexiscan on Other Drugs

Lexiscan is not known to inhibit the metabolism of substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in human liver microsomes, indicating that it is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:
There are no adequate well-controlled studies with Lexiscan in pregnant women. Lexiscan should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Reproductive studies in rats showed that regadenoson doses 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area, caused reduced fetal body weights and significant ossification delays in fore- and hind limb phalanges and metatarsals; however, maternal toxicity also occurred at these doses. Skeletal variations were increased in all treated groups. In rabbits, there were no teratogenic effects in offspring at regadenoson doses 4 times the MRHD, although signs of maternal toxicity occurred at this dose. At regadenoson doses equivalent to 12 and 20 times the MRHD, maternal toxicity occurred along with increased embryo-fetal loss and fetal malformations. It is not clear whether malformations that occurred at maternally toxic doses of regadenoson in both animal species were due to fetal drug effects or only to the maternal toxic effects.

Because animals received repeated doses of regadenoson, their exposure was significantly higher than that achieved with the standard single dose administered to humans [*see Animal Toxicology and Pharmacology* (13.2)].

8.3 Nursing Mothers

It is not known whether Lexiscan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Lexiscan in nursing infants, the decision to interrupt nursing after administration of Lexiscan or not to administer Lexiscan, should take into account the importance of the drug to the mother. Based on the pharmacokinetics of Lexiscan, it should be cleared 10 hours after administration. Therefore, nursing women may consider interrupting nursing for 10 hours after administration.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients (< 18 years of age) have not been established.

8.5 Geriatric Use

Of the 1,337 patients receiving Lexiscan in Studies 1 and 2, 56% were 65 years of age and over and 24% were 75 years of age and over. Older patients (≥ 75 years of age) had a similar

adverse event profile compared to younger patients (< 65 years of age), but had a higher incidence of hypotension (2% vs. < 1%).

10 OVERDOSAGE

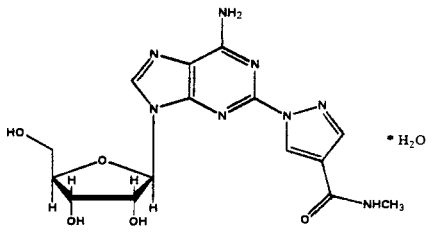
Lexiscan overdosage may result in serious reactions [*see Warnings and Precautions* (5)]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at Lexiscan doses greater than 0.02 mg/kg.

Aminophylline to Reverse Effects

Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30–60 seconds) to attenuate severe and/or persistent adverse reactions to Lexiscan.

11 DESCRIPTION

Regadenoson is an A_{2A} adenosine receptor agonist that is a coronary vasodilator [*see Clinical Pharmacology* (12.1)]. Regadenoson is chemically described as adenosine, 2-[4-[(methylamino)carbonyl]-1*H*-pyrazol-1-yl]-, monohydrate. Its structural formula is:



The molecular formula for regadenoson is $C_{15}H_{18}N_8O_5 \cdot H_2O$ and its molecular weight is 408.37.

Lexiscan is a sterile, nonpyrogenic solution for intravenous injection. The solution is clear and colorless. Each 1 mL in the 5-mL vial or pre-filled syringe contains 0.084 mg of regadenoson monohydrate, corresponding to 0.08 mg regadenoson on an anhydrous basis, 10.9 mg dibasic sodium phosphate dihydrate or 8.7 mg dibasic sodium phosphate anhydrous, 5.4 mg monobasic sodium phosphate monohydrate, 150 mg propylene glycol, 1 mg edetate disodium dihydrate, and Water for Injection, with pH between 6.3 and 7.7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regadenoson is a low affinity agonist ($K_i \approx 1.3$ μM) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A_1 adenosine receptor ($K_i > 16.5$ μM), and weak, if any, affinity for the A_{2B} and A_3 adenosine receptors. Activation of the A_{2A} adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow (CBF).

12.2 Pharmacodynamics

- Coronary Blood Flow

Lexiscan causes a rapid increase in CBF which is sustained for a short duration. In patients undergoing coronary catheterization, pulsed-wave Doppler ultrasonography was used to measure the average peak velocity (APV) of coronary blood flow before and up to 30 minutes after administration of regadenoson (0.4 mg, intravenously). Mean APV increased to greater than twice baseline by 30 seconds and decreased to less than twice the baseline level within 10 minutes [*see Clinical Pharmacology* (12.3)].

Myocardial uptake of the radiopharmaceutical is proportional to CBF. Because Lexiscan increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Lexiscan causes relatively less uptake of the radiopharmaceutical in vascular territories supplied by stenotic arteries. MPI intensity after Lexiscan administration is therefore greater in areas perfused by normal relative to stenosed arteries.

Effect of Aminophylline

Aminophylline (100 mg, administered by slow iv injection over 60 seconds) injected 1 minute after 0.4 mg Lexiscan in subjects undergoing cardiac catheterization, was shown to shorten the duration of the coronary blood flow response to Lexiscan as measured by pulsed-wave Doppler ultrasonography [*see Overdosage* (10)].

Effect of Caffeine

A placebo-controlled clinical study assessed the effects of oral caffeine (200 mg) on the regadenoson-induced increase in coronary flow reserve (CFR) using positron emission tomography (PET) with radiolabeled water. Healthy subjects took caffeine 200 mg orally or placebo approximately 2 hours prior to Lexiscan administration. Following Lexiscan administration, the median CFR in caffeinated subjects was 92% of the CFR in non-caffeinated subjects [*see Drug Interactions* (7.1) *and Patient Counseling Information* (17.1)].

- Hemodynamic Effects

In clinical studies, the majority of patients had an increase in heart rate and a decrease in blood pressure within 45 minutes after administration of Lexiscan. Maximum hemodynamic changes after Lexiscan or Adenoscan in Studies 1 and 2 are summarized in Table 3.

Table 3

Hemodynamic Effects in Studies 1 and 2

Vital Sign Parameter	Lexiscan N = 1,337	Adenoscan N = 678
Heart Rate		
>100 bpm	22%	13%
increase > 40 bpm	5%	3%
Systolic Blood Pressure		
< 90 mm Hg	2%	3%
decrease >35 mm Hg	7%	8%
Diastolic Blood Pressure		
< 50 mm Hg	2%	4%
decrease >25 mm Hg	4%	5%

- Respiratory Effects

The A_{2B} and A_3 adenosine receptors have been implicated in the pathophysiology of bronchoconstriction in susceptible individuals (i.e., asthmatics). In *in vitro* studies, regadenoson has not been shown to have appreciable binding affinity for the A_{2B} and A_3 adenosine receptors.

12.3 Pharmacokinetics

In healthy volunteers, the regadenoson plasma concentration-time profile is multi-exponential in nature and best characterized by 3-compartment model. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes after injection of Lexiscan and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2 to 4 minutes. An intermediate phase follows, with a half-life on average of 30 minutes coinciding with loss of the pharmacodynamic effect. The terminal phase consists of a decline in plasma concentration with a half-life of approximately 2 hours [*see Clinical Pharmacology* (12.2)]. Within the dose range of 0.3–20 μg/kg in healthy subjects, clearance, terminal half-life or volume of distribution do not appear dependent upon the dose.

A population pharmacokinetic analysis including data from subjects and patients demonstrated that regadenoson clearance decreases in parallel with a reduction in creatinine clearance and clearance increases with increased body weight. Age, gender, and race have minimal effects on the pharmacokinetics of regadenoson.

Special Populations

Renally Impaired Patients: The disposition of regadenoson was studied in 18 subjects with various degrees of renal function and in 6 healthy subjects. With increasing renal impairment, from mild (CLcr 50 to < 80 mL/min) to moderate (CLcr 30 to < 50 mL/min) to severe renal impairment (CLcr < 30 mL/min), the fraction of regadenoson excreted

unchanged in urine and the renal clearance decreased, resulting in increased elimination half-lives and AUC values compared to healthy subjects (CLcr ≥ 80 mL/min). However, the maximum observed plasma concentrations as well as volumes of distribution estimates were similar across the groups. The plasma concentration-time profiles were not significantly altered in the early stages after dosing when most pharmacologic effects are observed. No dose adjustment is needed in patients with renal impairment.

Patients with End Stage Renal Disease: The pharmacokinetics of regadenoson in patients on dialysis has not been assessed.

Hepatically Impaired Patients: The influence of hepatic impairment on the pharmacokinetics of regadenoson has not been evaluated. Because greater than 55% of the dose is excreted in the urine as unchanged drug and factors that decrease clearance do not affect the plasma concentration in the early stages after dosing when clinically meaningful pharmacologic effects are observed, no dose adjustment is needed in patients with hepatic impairment.

Geriatric Patients: Based on a population pharmacokinetic analysis, age has a minor influence on the pharmacokinetics of regadenoson. No dose adjustment is needed in elderly patients.

Metabolism

The metabolism of regadenoson is unknown in humans. Incubation with rat, dog, and human liver microsomes as well as human hepatocytes produced no detectable metabolites of regadenoson.

Excretion

In healthy volunteers, 57% of the regadenoson dose is excreted unchanged in the urine (range 19–77%), with an average plasma renal clearance around 450 mL/min, i.e., in excess of the glomerular filtration rate. This indicates that renal tubular secretion plays a role in regadenoson elimination.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Regadenoson was negative in the Ames bacterial mutation assay, chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and mouse bone marrow micronucleus assay.

Long-term animal studies have not been conducted to evaluate Lexiscan's carcinogenic potential or potential effects on fertility.

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies

Reproduction studies were conducted in rabbits and rats using doses of Lexiscan that were 2 to 20 times (rats) and 4 to 20 times (rabbits) the maximum recommended human dose (MRHD), based on body surface area comparison.

When administered to rabbits during organogenesis, regadenoson caused maternal toxicity including tachypnea, soft, liquid or scant feces, and localized alopecia in all treated groups, and caused reduction in body weight and feed consumption at 0.3 and 0.5 mg/kg/day (12 and 20 X MRHD, respectively). At regadenoson doses equivalent to 12 and 20 times the MRHD, maternal toxicity occurred along with decreased number of live fetuses, reduced fetal body weight, and occurrence of fetal variations and malformations. At regadenoson doses equivalent to 20 times the MRHD, resorptions were increased and fetal body weights reduced. Fetal malformations included microphthalmia (1/116 at 20 X MRHD), interrelated vertebrae/rib alterations (2/145 and 2/116 each at 12 and 20 X MRHD), and misaligned caudal vertebrae (3/145 at 12 X MRHD). Fetal toxicity was only observed at maternally toxic doses. The no effect dose level for fetal toxicity is 0.1 mg/kg (4 X MRHD). A no effect dose level was not identified for maternal toxicity.

When regadenoson was administered to pregnant rats during the period of major organogenesis, 4/25 rats from the 1.0 mg/kg/day group (20 X MRHD) and 1/25 rats from the 0.8 mg/kg (16 X MRHD) group died immediately following the first dose of regadenoson. All dams had decreased motor activity and one was gasping post-dosing. At doses $\geq$ 0.5 mg/kg (10 X MRHD), maternal toxicity included decreased motor activity, increased limb extension, excess salivation, and reduction in body weight and feed consumption. At doses $\geq$ 0.5 mg/kg, fetal body weights were significantly reduced and significant ossification delays were observed in fore- and hindlimb phalanges and metatarsals. Skeletal malformations included delayed ossification of the skull (1/167), and hemivertebra present at a thoracic vertebra (1/167), observed at 16-20 X MRHD, and small arches of a lumbar and sacral vertebrae (1/174) observed at 2 X MRHD. The no effect dose level for maternal toxicity is 0.1 mg/kg/day (2 X MRHD).

Cardiomyopathy

Minimal cardiomyopathy (myocyte necrosis and inflammation) was observed in rats following single dose administration of regadenoson. Increased incidence of minimal cardiomyopathy was observed on day 2 in males at doses of 0.08, 0.2 and 0.8 mg/kg (1/5, 2/5, and 5/5) and in females (2/5) at 0.8 mg/kg. In a separate study in male rats, the mean arterial pressure was decreased by 30 to 50% of baseline values for up to 90 minutes at regadenoson doses of 0.2 and 0.8 mg/kg, respectively. No cardiomyopathy was noted in rats sacrificed 15 days following single administration of regadenoson. The mechanism of the cardiomyopathy induced by regadenoson was not elucidated in this study but was associated with the hypotensive effects of regadenoson. Profound hypotension induced by vasoactive drugs is known to cause cardiomyopathy in rats.

Local Irritation

Intravenous administration of Lexiscan to rabbits resulted in perivascular hemorrhage, vein vasculitis, inflammation, thrombosis and necrosis, with inflammation and thrombosis persisting through day 8 (last observation day). Perivascular administration of Lexiscan to rabbits resulted in hemorrhage, inflammation, pustule formation and epidermal hyperplasia, which persisted through day 8 except for the hemorrhage which resolved. Subcutaneous administration of Lexiscan to rabbits resulted in hemorrhage, acute inflammation, and necrosis; on day 8 muscle fiber regeneration was observed.

14 CLINICAL STUDIES

The efficacy and safety of Lexiscan were determined relative to Adenoscan in two randomized, double-blind studies (Studies 1 and 2) in 2,015 patients with known or suspected coronary artery disease who were indicated for pharmacologic stress MPI. A total of 1,871 of these patients had images considered valid for the primary efficacy evaluation, including 1,294 (69%) men and 577 (31%) women with a median age of 66 years (range 26-93 years of age). Each patient received an initial stress scan using Adenoscan (6-minute infusion using a dose of 0.14 mg/kg/min, without exercise) with a radionuclide gated SPECT imaging protocol. After the initial scan, patients were randomized to either Lexiscan or Adenoscan, and received a second stress scan with the same radionuclide imaging protocol as that used for the initial scan. The median time between scans was 7 days (range of 1–104 days).

The most common cardiovascular histories included hypertension (81%), CABG, PTCA or stenting (51%), angina (63%), and history of myocardial infarction (41%) or arrhythmia (33%); other medical history included diabetes (32%) and COPD (5%). Patients with a recent history of serious uncontrolled ventricular arrhythmia, myocardial infarction, or unstable angina, a history of greater than 1st degree AV block, or with symptomatic bradycardia, sick sinus syndrome, or a heart transplant were excluded. A number of patients took cardioactive medications on the day of the scan, including β-blockers (18%), calcium channel blockers (9%), and nitrates (6%). In the pooled study population, 68% of patients had 0–1 segments showing reversible defects on the initial scan, 24% had 2–4 segments, and 9% had ≥ 5 segments.

Image Agreement

Comparison of the images obtained with Lexiscan to those obtained with Adenoscan was performed as follows. Using the 17-segment model, the number of segments showing a reversible perfusion defect was calculated for the initial Adenoscan study and for the randomized study obtained using Lexiscan or Adenoscan. The agreement rate for the image obtained with Lexiscan or Adenoscan relative to the initial Adenoscan image was calculated by determining how frequently the patients assigned to each initial Adenoscan category (0–1, 2–4, 5–17 reversible segments) were placed in the same category with the randomized scan. The agreement rates for Lexiscan and Adenoscan were calculated as the average of the agreement rates across the three categories determined by the initial scan. Studies 1 and 2

each demonstrated that Lexiscan is similar to Adenoscan in assessing the extent of reversible perfusion abnormalities (Table 4).

Table 4

Agreement Rates in Studies 1 and 2

	Study 1	Study 2
Adenoscan – Adenoscan Agreement Rate (± SE)	61 ± 3%	64 ± 4%
Adenoscan – Lexiscan Agreement Rate (± SE)	62 ± 2%	63 ± 3%
Rate Difference (Lexiscan – Adenoscan) (± SE)	1 ± 4%	-1 ± 5%
95% Confidence Interval	-7.5, 9.2%	-11.2, 8.7%

16 HOW SUPPLIED/STORAGE AND HANDLING

Lexiscan is supplied as a sterile, preservative-free solution containing 0.08 mg/mL regadenoson in the following packages:

- Single-use 5 mL vials (NDC 0469-6501-05).
- Single-use 5 mL pre-filled plastic Ansyr® syringes with luer-lock fitting (NDC 0469-6501-89).

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59°–86°F).

17 PATIENT COUNSELING INFORMATION

17.1 Methylxanthine Consumption

Patients should be instructed to avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products, and theophylline for at least 12 hours before a scheduled radionuclide MPI.

17.2 Common Reactions

Prior to Lexiscan administration, patients should be informed of the most common reactions (such as shortness of breath, headache and flushing) that have been reported in association with Lexiscan during MPI.

17.3 Patients with COPD or Asthma

Patients with COPD or asthma should be informed to discuss their respiratory history and administration of pre-and post-study bronchodilator therapy with their clinician before scheduling an MPI study with Lexiscan.

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