In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in patients post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37% on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment.

The safety and efficacy of vardenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Vardenafil is rapidly absorbed with maximum observed plasma concentrations reached in some men as early as 15 minutes after oral administration. However, 90% of the time, maximum plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 15 %. After oral dosing of vardenafil AUC and C_{max} increase almost dose proportionally over the recommended dose range (5 – 20 mg).

When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median t_{max} of 1 hour and a mean reduction in C_{max} of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (t_{max}, C_{max} and AUC) are unchanged compared to administration under fasting conditions.

Distribution

The mean steady state volume of distribution for vardenafil is 208 l, indicating distribution into the tissues. Vardenafil and its major circulating metabolite (M1) are highly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as M1, protein binding is independent of total drug concentrations.

Based on measurements of vardenafil in semen of healthy subjects 90 minutes after dosing, not more than 0.00012% of the administered dose may appear in the semen of patients.

Metabolism

Vardenafil is metabolised predominantly by hepatic metabolism via cytochrome P450 (CYP) isoform 3A4 with some contribution from CYP3A5 and CYP2C isoforms.

In humans the one major circulating metabolite (M1) results from desethylation of vardenafil and is subject to further metabolism with a plasma elimination half life of approximately 4 hours. Parts of

M1 are in the form of the glucuronide in systemic circulation. Metabolite M1 shows a phosphodiesterase selectivity profile similar to vardenafil and an *in vitro* potency for phosphodiesterase type 5 of approximately 28% compared to vardenafil, resulting in an efficacy contribution of about 7%.

Elimination

The total body clearance of vardenafil is 56 l/h with a resultant terminal half life of approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the faeces (approximately 91-95% of the administered dose) and to a lesser extent in the urine (approximately 2-6% of the administered dose).

Pharmacokinetics in special patient groups

Elderly
Hepatic clearance of vardenafil in healthy elderly volunteers (65 years and over) was reduced as compared to healthy younger volunteers (18 - 45 years). On average elderly males had a 52% higher AUC, and a 34% higher C_{max} than younger males (see Section 4.2).

Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance 30 – 80 ml/min), the pharmacokinetics of vardenafil were similar to that of a normal renal function control group. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min) the mean AUC was increased by 21% and the mean Cmax decreased by 23%, compared to volunteers with no renal impairment. No statistically significant correlation was observed between creatinine clearance and vardenafil exposure (AUC and C_{max}) (see Section 4.2). Vardenafil pharmacokinetics have not been studied in patients requiring dialysis (see section 4.3).

Hepatic insufficiency
In patients with mild to moderate hepatic impairment (Child-Pugh A and B), the clearance of vardenafil was reduced in proportion to the degree of hepatic impairment. In patients with mild hepatic impairment (Child-Pugh A), the mean AUC and C_{max} increased 17% and 22% respectively, compared to healthy control subjects. In patients with moderate impairment (Child-Pugh B), the mean AUC and C_{max} increased 160% and 133% respectively, compared to healthy control subjects (see Section 4.2). The pharmacokinetics of vardenafil in patients with severely impaired hepatic function (Child-Pugh C) have not been studied (see Section 4.3).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Crospovidone,
Magnesium Stearate,
Microcrystalline cellulose,
Silica, colloidal anhydrous.

Film coat:
Macrogol 400,

Hypromellose,
Titanium dioxide (E171),
Ferric oxide yellow (E172),
Ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG,
D-51368 Leverkusen,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

バルデナフィルとα遮断薬の併用禁忌措置に関する、米国における対応状況

米国では，2003年8月19日に承認されたが，その際にはα遮断薬を投与中の患者は禁忌とされ，承認時におけるPhase IV commitmentsとして，本薬とα遮断薬との相互作用に関する臨床薬理試験を追加実施することが計画されていた。しかしながら，その後，承認時に実施中であった臨床薬理試験（試験No.100547）の成績，第II相から第IV相臨床試験で得られた安全性データの統合解析結果及び市販後の使用成績調査結果等をFDAに提出し，本薬とα遮断薬との併用投与に関する協議を行った結果，2005年5月13日に，α遮断薬を投与中の患者を禁忌から外すことが了承された。

その詳細な経緯及びFDAとの協議内容を以下に示します。

米国では，本薬の承認時（2003年8月19日）に，「健康成人男子を対象としたα遮断薬との相互作用試験」（試験No.100480及び試験No.100481）の成績に基づいて，FDAよりα遮断薬を投与中の患者が「禁忌」とされ，Phase IV commitmentとして，本薬2.5 mgのα遮断薬との相互作用試験及びタムロシンとテラゾシン以外のα遮断薬との相互作用試験の2試験を追加実施することが指示されました。

その後，承認の直前に得られていた「α遮断薬（タムスロシンとテラゾシン）による治療で安定している良性前立腺肥大症患者を対象とした相互作用試験（試験No.100535）」の成績に加えて，承認当時実施中であった「α遮断薬（タムスロシン）による治療で安定している良性前立腺肥大症患者を対象とした相互作用試験（試験No.100547）」の成績が新たに得られました。これら2試験の成績から，α遮断薬による治療で安定している患者では，本薬との併用による血圧の低下は僅かであり，忍容性も良好であることが確認されたことから，2003年12月22日にこれら試験成績がFDAに提出され，本薬のα遮断薬との併用投与に関する協議が改めて開始されました。

米国・バイエル社とFDAとの間で行われた一連の協議に関する概略を以下に示します。

<u>2004年3月2日　第1回目の会議</u>

新たに提出した良性前立腺肥大症患者を対象とした相互作用試験2試験の成績が，本薬とα遮断薬との併用投与の可否及びα遮断薬と併用する場合の本薬の適切な用量を検討するために十分な情報であると考えるか，Phase IV commitmentとして指示されたα遮断薬との相互作用試験の追加実施がやはり必要であるかについて，FDAに照会した。また，添付文書におけるα遮断薬を投与中の患者を「禁忌」から外し，併用投与に関して下記のような注意事項を追記することを提案した。

- 本薬はα遮断薬であるタムスロシン0.4 mgと併用することができる。
- タムスロシン以外のα遮断薬と併用する際には本薬の用量は5 mgを超えないこと。また，α遮断薬の投与から6時間以内の投与は避けること。
- α遮断薬による治療で患者の状態が安定している場合のみ，本薬との併用投与を開始すること。

その結果，本薬とα遮断薬との併用投与に関する添付文書改訂の提案も含めた米国・バイエル社からの照会事項に対して，FDAから明確な回答は得られなかったが，「併用禁忌」の根拠となった「健康成人男子を対象としたα遮断薬との相互作用試験」（試験No. 100480及び試験No. 100481）は，健康成人男子にα遮断薬を強制的に高用量まで漸増したものであり，これらの成績は両剤の併用投与により実地臨床上起こり得る血圧低下のリスクを反映するものではないとの主張に対して同意が得られ，引き続きFDA内部で本件に関する検討を行うことが約束された。

また，α遮断薬との併用投与に関するPhase IVcommitment（2試験）については，上述の確認事項に対するFDAの回答が得られるまで，その実施を延期することが両者で合意された。

<u>2004年3月25日　第2回目の会議</u>

前回，米国・バイエル社が照会した事項に対するFDAの回答が得られた。

1） 新たに提出した良性前立腺肥大症患者を対象とした相互作用試験（試験No. 100535及び試験No. 100547）の成績が，本薬とα遮断薬との併用投与時の本薬の適切な用量を検討するために十分な情報であると考えるか？

＜回答＞

タムスロシンと併用投与した際の立位収縮期血圧における血圧低下のアウトライヤー（最低収縮期血圧が85 mmHg以下）をみると，本薬10又は20 mg投与時（試験No. 100547）と比較して，5 mg投与時（試験No. 100535）で多く認められており，用量依存性が明らかでないこと，また，一般的にテラゾシンがより強力なα遮断薬と考えられているが，タムスロシンとの併用時の方がテラゾシンとの併用時よりも立位収縮期血圧でアウトライヤーが多くみられた（試験No. 100535）ことから，現時点ではα遮断薬との併用投与時における本薬の適切な用量を見出すことはできない。

2） 良性前立腺肥大症患者を対象とした相互作用試験（試験No. 100547）試験の成績を以って，Phase IV commitmentとして要求されている本薬2.5 mgとα遮断薬との相互作用試験の追加実施を再考して頂けるか？

＜回答＞

α遮断薬との併用投与を安全に行えるか否かを判断するためには，本薬の承認用量である5 mg，10 mg及び20 mgとα遮断薬との併用投与に関する安全性データが更に必要と考える。本薬2.5 mgを用いた相互作用試験が必要か否かは，5～20 mgにおける成績次第である。これらの用量で安全であることが明らかになれば，本薬2.5 mgとα遮断薬との相互作用試験を免除することを考慮することになるであろう。

さらに，FDAから，α遮断薬との併用投与時における本薬の適切な用量を設定するために

は，追加試験が必要と考えられるが，プラセボを対照とした並行群間比較により各群最低20症例で検討されるべきであること，市販後の使用成績調査に基づくα遮断薬との併用投与に関する安全性データが提出された際には，その成績も考慮するとのコメントを得た。

2004年7月21日　第3回目の協議

米国・バイエル社は，2004年4月26日に社外の専門家を招聘してExpert Meetingを開催し，これまでに得られた本薬のα遮断薬との相互作用試験成績，欧米で実施中の市販後使用成績調査の中間結果等を基に，本薬とα遮断薬との併用投与に関する安全性を討議した結果，得られた以下の見解をFDAに報告した。

- 本薬の血圧低下作用には，治療用量の範囲内で用量反応性がみられておらず，α遮断薬と併用投与した際の血圧低下に対する相互作用は，相乗的ではなく，相加的である。
- これまでに得られた相互作用試験の成績から，本薬と検討されたα遮断薬との間で血圧低下に関して重大な相互作用がないことが示されており，本薬5～20 mgを用いた追加試験を実施しても新たな知見は得られないであろう。
- 試験100535で本薬とタムスロシンを併用投与した良性前立腺肥大症患者にみられた無症候性で一過性の立位収縮期血圧の低下（併用後の血圧値：80～85 mmHg）は，臨床的に意味のあるリスクとは言えないと考える。

さらに，上述の見解に加えて，欧米で実施中である市販後使用成績調査の中間結果においても，本薬とα遮断薬が併用投与された症例で非併用例に比して臨床上のリスクが高くなる傾向は認められていないことから，本薬の添付文書の「使用上の注意」の項に，①本薬の5～20 mgはタムスロシン0.4 mgと投与間隔に関わらず併用することが可能であること，②その他のα遮断薬では本薬5 mgを6時間の間隔をあけて投与すること，③本薬が併用される前に，α遮断薬による治療で患者の状態が安定していること，を「使用上の注意」の項に記載した上で，α遮断薬を投与中の患者を「禁忌」から外すことを再度提案した。

その結果，FDAから，Phase IV commitmentとして要求したα遮断薬との相互作用試験を追加実施せずに，α遮断薬を投与中の患者を「禁忌」から外せる可能性はあり，他のPDE5阻害剤の添付文書における記載内容も含めて検討する旨の回答が得られると共に，その結論が出るまで，本薬2.5 mgにおけるα遮断薬との相互作用試験の実施を延期することに対しても同意が得られた。

2004年9月15日　第4回目の協議

FDAは，既に承認されている本薬を含むPDE5阻害剤3剤の添付文書において，α遮断薬との併用投与に関する注意事項の記載がそれぞれ異なっていることが，医療従事者や患者に混乱を招いていることを認め，これら薬剤の添付文書の記載を再検討する必要性があると考え，以下の結論に達したことを米国・バイエル社に伝達した。

- 現在までに承認したPDE5阻害剤の各添付文書におけるα遮断薬との併用投与に関する注意事項の記載が異なるのは妥当ではない。

- これらPDE5阻害剤において，α遮断薬を投与中の患者を「禁忌」にする必要はない。
- α遮断薬との併用投与に関しては，3薬剤とも「使用上の注意」の項に同様の記載を行うこととし，FDAがその原案を作成する。
- 「使用上の注意」の“薬物相互作用”の項に，α遮断薬との併用投与に関連するすべての臨床薬理試験成績を記載する。

2004年10月20日に，FDAから添付文書の原案が提示され，FDAがそれぞれPDE5阻害剤を販売する製薬会社と記載内容に関する調整等を行った後，2005年5月13日にα遮断薬を投与中の患者を「禁忌」から外すことが了承され，添付文書中の「使用上の注意」及び「用法・用量」の項に表4に示す内容を記載することになった。

表4　米国の添付文書におけるα遮断薬との併用投与に関する記載

(原文)

PRECAUTION

Alpha-blockers: Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. Phosphodiesterase Type 5 (PDE5) inhibitors, including LEVITRA, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see PRECAUTIONS, Drug Interactions) leading to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

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

DOSAGE and ADMINISTRATION

·····. For alpha-blockers, caution is advised when PDE5 inhibitors, including LEVITRA, are used concomitantly with alpha-blockers because of the potential for an additive effect on blood pressure. In some patients, concomitant use of these two drug classes can lower blood pressure significantly (see PRECAUTIONS, Alpha-blockers and Drug Interactions) leading to symptomatic hypotension (e.g., fainting). Concomitant treatment should be initiated only if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, LEVITRA should be initiated at a dose of 5 mg (2.5 mg when used concomitantly with certain CYP3A4 inhibitors - see Drug Interactions).

(和訳)

使用上の注意

α遮断薬：PDE5阻害薬とα遮断薬を併用する場合には注意が必要である。レビトラを含むPDE5阻害薬とα遮断薬はともに降圧作用を有する血管拡張薬である。血管拡張薬を組み合わせて使用する場合には，血圧に対する相加的作用がみられる可能性がある。患者によっては，これら2つのクラスの薬剤を併用することにより，血圧を著しく低下させ，症候性低血圧（失神等）を起こす場合がある（「使用上の注意」の「薬物相互作用」参照）。以下の事項に注意すること。

・PDE5阻害薬の投与を開始する前に，α遮断薬による治療で安定していること。α遮断薬の単独療法に対して血行動態が不安定な患者では，PDE5阻害薬の併用により症候性低血圧のリスクが増加する。
・α遮断薬による治療で安定している患者にPDE5阻害薬を投与する場合には，最低推奨用量から開始すること（「用法・用量」参照）。
・PDE5阻害薬の適正用量が既に投与されている患者では，α遮断薬による治療は最低用量から開始すること。

PDE5阻害薬が投与されている患者でα遮断薬を段階的に増量すると，さらに血圧が低下する可能性がある。
・PDE5 阻害薬と α 遮断薬との併用時における安全性は，血管内容量の減少や他の降圧剤等により影響を受ける可能性がある。

用法・用量

……。α 遮断薬について，レビトラを含むPDE5阻害薬が α 遮断薬と併用投与される場合には，血圧に対する相加的作用がみられる可能性があるため，注意が必要である。患者によっては，これら2つのクラスの薬剤を併用することにより，血圧を著しく低下させ，症候性低血圧（失神等）を起こす場合がある（「**使用上の注意**」の「**α 遮断薬**」及び「**薬物相互作用**」参照）。患者が α 遮断薬による治療で安定している場合のみ，併用投与を開始すること。α 遮断薬による治療で安定している患者に対して，レビトラは5 mgから投与を開始すること（CYP3A4阻害薬が併用されている場合には2.5 mg，「**薬物相互作用**」参照）。

なお，Phase IV commitmentであったα遮断薬との相互作用試験については，FDAと引き続き協議が行われていたが，最近，アルフゾシンとの相互作用試験を1試験実施することで同意が得られ，現在試験実施計画書の調整が行われており，来年実施される予定である。

その後，米国でα遮断薬を投与中の患者を「禁忌」から外すことが了承され，添付文書が改訂されたことに伴い，2006年2月14日にCompany Core Data Sheet（CCDS）が改訂されました（**表5**）。

表5　CCDSにおける α 遮断薬との併用に関する記載

（原文）

SPECIAL WARNING AND PRECAUTION

Consistent with vasodilatory effects of alpha-blockers and vardebafil, the concomitant use of vardenafil with alpha-blockers may lead to symptomatic hypotension in some patients. Concomitant treatment should only be initiated if the patient is stable on his alpha-blocker therapy. In those patients who are stable on alpha-blocker therapy, vardenafil should be initiated at the lowest recommended starting dose of 5 mg. Vardenafil may be administered at any time with tamsulosin. With other alpha-blockers a time separation of dosing should be considered when vardenafil is prescribed concomitantly. In those patients already taking an optimized dose of vardenafil, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure in patients taking a PDE5 inhibitor including vardenafif.

POSOLOGY AND METHOD OF ADMINISTRATION,

(Same as the above)

（和訳）

警告及び使用上の注意

α遮断薬とバルデナフィルはともに血管拡張作用を有することから，バルデナフィルとα遮断薬を併用すると，症候性低血圧に至る場合がある。α遮断薬による治療が安定している患者に限り，バルデナフィルとの併用を開始するべきである。α遮断薬による治療で安定している患者では，最低推奨用量の5 mgから投与を開始するべきである。バルデナフィルはタムスロシンと投与間隔に関わらず併用してもよい。その他のα遮断薬では，バルデナフィルが併用処方された場合，投与間隔を考慮するべきである。既にバルデナフィルの適正用量が投与されている患者では，α遮断薬は最低用量から開始するべきである。バルデナフィルが投与されている患者でα遮断薬を段階的に増量すると，さらに血圧が低下する可能性がある。

用法・用量

（上記と同一内容）

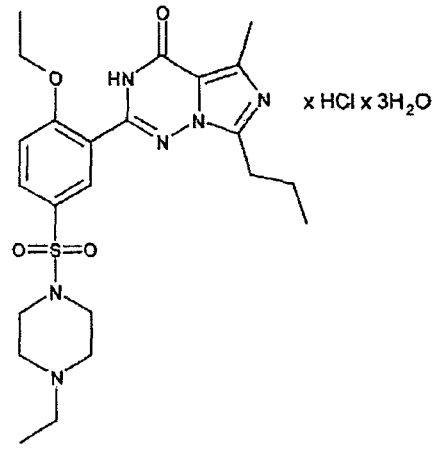
LEVITRA®
(vardenafil HCl)
TABLETS

08918646, R.3 3/07

DESCRIPTION

LEVITRA® is an oral therapy for the treatment of erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Vardenafil HCl is designated chemically as piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride and has the following structural formula:



Vardenafil HCl is a nearly colorless, solid substance with a molecular weight of 579.1 g/mol and a solubility of 0.11 mg/mL in water. LEVITRA is formulated as orange, round, film-coated tablets with "BAYER" cross debossed on one side and "2.5", "5", "10", and "20" on the other side corresponding to 2.5 mg, 5 mg, 10 mg, and 20 mg of vardenafil, respectively. In addition to the active ingredient, vardenafil HCl, each tablet contains microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

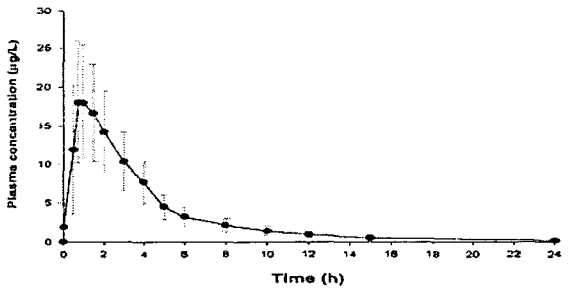
Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most

abundant PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5); therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.
In vitro studies have shown that vardenafil is a selective inhibitor of PDE5. The inhibitory effect of vardenafil is more selective on PDE5 than for other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1,000-fold relative to PDE2, 3, 4, 7, 8, 9, and 10).

Pharmacokinetics

The pharmacokinetics of vardenafil are approximately dose proportional over the recommended dose range. Vardenafil is eliminated predominantly by hepatic metabolism, mainly by CYP3A4 and to a minor extent, CYP2C isoforms. Concomitant use with potent CYP3A4 inhibitors such as ritonavir, indinavir, ketoconazole, as well as moderate CYP3A inhibitors such as erythromycin results in significant increases of plasma levels of vardenafil (see **PRECAUTIONS, WARNINGS** and **DOSAGE AND ADMINISTRATION**). Mean vardenafil plasma concentrations measured after the administration of a single oral dose of 20 mg to healthy male volunteers are depicted in Figure 1.

Figure 1: Plasma Vardenafil Concentration (Mean ± SD) Curve for a Single 20 mg LEVITRA Dose



Absorption: Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15%. Maximum observed plasma concentrations after a single 20 mg dose in healthy volunteers are usually reached between 30 minutes and 2 hours (median 60 minutes) after oral dosing in the fasted state. Two food-effect studies were conducted which showed that high-fat meals caused a reduction in C_{max} by 18%-50%.
Distribution: The mean steady-state volume of distribution (Vss) for vardenafil is 208 L, indicating extensive tissue distribution. Vardenafil and its major circulating metabolite, M1, are highly bound to plasma proteins (about 95% for parent drug and M1). This protein binding is reversible and independent of total drug concentrations.
Following a single oral dose of 20 mg vardenafil in healthy volunteers, a mean of 0.00018% of the administered dose was obtained in semen 1.5 hours after dosing.

Metabolism: Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. M1 is subject to further metabolism. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity.

Excretion: The total body clearance of vardenafil is 56 L/h, and the terminal half-life of vardenafil and its primary metabolite (M1) is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose).

Pharmacokinetics in Special Populations

Pediatrics: Vardenafil trials were not conducted in the pediatric population.

Geriatrics: In a healthy volunteer study of elderly males (≥65 years) and younger males (18–45 years), mean C_{max} and AUC were 34% and 52% higher, respectively, in the elderly males (see **PRECAUTIONS, Geriatric Use** and **DOSAGE AND ADMINISTRATION**). Consequently, a lower starting dose of LEVITRA (5 mg) in patients ≥65 years of age should be considered.

Renal Insufficiency: In volunteers with mild renal impairment (CL_{cr} = 50-80 ml/min), the pharmacokinetics of vardenafil were similar to those observed in a control group with normal renal function. In the moderate (CL_{cr} = 30-50 ml/min) or severe (CL_{cr} <30 ml/min) renal impairment groups, the AUC of vardenafil was 20–30% higher compared to that observed in a control group with normal renal function (CL_{cr} >80 ml/min). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis (see **PRECAUTIONS, Renal Insufficiency,** and **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: In volunteers with mild hepatic impairment (Child-Pugh A), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 22% and 17%, respectively, compared to healthy control subjects. In volunteers with moderate hepatic impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Consequently, a starting dose of 5 mg is recommended for patients with moderate hepatic impairment, and the maximum dose should not exceed 10 mg (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment.

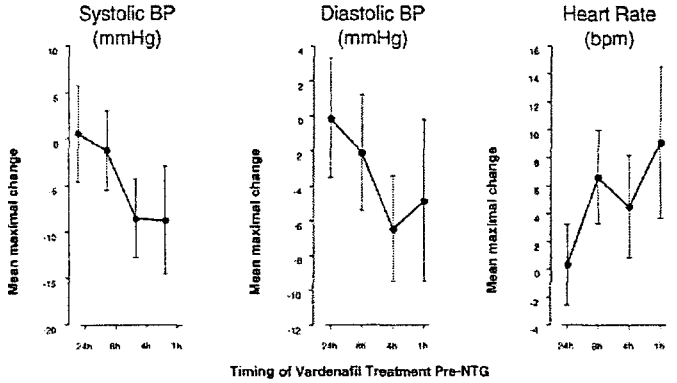
Pharmacodynamics

Effects on Blood Pressure: In a clinical pharmacology study of patients with erectile dysfunction, single doses of vardenafil 20 mg caused a mean maximum decrease in supine blood pressure of 7 mmHg systolic and 8 mmHg diastolic (compared to placebo), accompanied by a mean maximum increase of heart rate of 4 beats per minute. The maximum decrease in blood pressure occurred between 1 and 4 hours after dosing. Following multiple dosing for 31 days, similar blood pressure responses were observed on Day 31 as on Day 1. Vardenafil may add to the blood pressure lowering effects of antihypertensive agents (see **PRECAUTIONS, Drug Interactions**).

Effects on Blood Pressure and Heart Rate when LEVITRA is Combined with Nitrates: A study was conducted in which the blood pressure and heart rate response to 0.4 mg nitroglycerin (NTG) sublingually was evaluated in 18 healthy subjects following pretreatment with LEVITRA 20 mg at various times before NTG administration. LEVITRA 20 mg caused an additional time-related reduction in blood pressure and increase in heart rate in association with NTG administration. The blood pressure effects were observed when LEVITRA 20 mg was dosed 1 or 4 hours before NTG and

the heart rate effects were observed when 20 mg was dosed 1, 4, or 8 hours before NTG. Additional blood pressure and heart rate changes were not detected when LEVITRA 20 mg was dosed 24 hours before NTG. (See Figure 2.)

Figure 2: Placebo-subtracted point estimates (with 90% CI) of mean maximal blood pressure and heart rate effects of pre-dosing with LEVITRA 20 mg at 24, 8, 4, and 1 hour before 0.4 mg NTG sublingually.



Because the disease state of patients requiring nitrate therapy is anticipated to increase the likelihood of hypotension, the use of vardenafil by patients on nitrate therapy or on nitric oxide donors is contraindicated (see **CONTRAINDICATIONS**).

Electrophysiology: The effect of 10 mg and 80 mg vardenafil on QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) crossover study in 59 healthy males (81% White, 12% Black, 7% Hispanic) aged 45-60 years. The QT interval was measured at one hour post dose because this time point approximates the average time of peak vardenafil concentration. The 80 mg dose of LEVITRA (four times the highest recommended dose) was chosen because this dose yields plasma concentrations covering those observed upon co-administration of a low-dose of LEVITRA (5 mg) and 600 mg BID of ritonavir. Of the CYP3A4 inhibitors that have been studied, ritonavir causes the most significant drug-drug interaction with vardenafil. Table 1 summarizes the effect on mean uncorrected QT and mean corrected QT interval (QT_c) with different methods of correction (Fridericia and a linear individual correction method) at one hour post-dose. No single correction method is known to be more valid than the other. In this study, the mean increase in heart rate associated with a 10 mg dose of LEVITRA compared to placebo was 5 beats/minute and with an 80 mg dose of LEVITRA the mean increase was 6 beats/minute.

Table 1. Mean QT and QT_c changes in msec (90% CI) from baseline relative to placebo at 1 hour post-dose with different methodologies to correct for the effect of heart rate.

Drug/Dose	QT Uncorrected (msec)	Fridericia QT Correction (msec)	Individual QT Correction (msec)
Vardenafil 10 mg	-2 (-4, 0)	8 (6, 9)	4 (3, 6)
Vardenafil 80 mg	-2 (-4, 0)	10 (8, 11)	6 (4, 7)
Moxifloxacin* 400 mg	3 (1, 5)	8 (6, 9)	7 (5, 8)

* Active control (drug known to prolong QT)

Therapeutic and supratherapeutic doses of vardenafil and the active control moxifloxacin produced similar increases in QT_c interval. This study, however, was not designed to make direct statistical comparisons between the drug or the dose levels. The clinical impact of these QT_c changes is unknown (see **PRECAUTIONS**).

In a separate postmarketing study of 44 healthy volunteers, single doses of 10 mg LEVITRA resulted in a placebo-subtracted mean change from baseline of QTcF (Fridericia correction) of 5 msec (90% CI: 2,8). Single doses of gatifloxacin 400mg resulted in a placebo-subtracted mean change from baseline QTcF of 4 msec (90% CI: 1,7). When LEVITRA 10mg and gatifloxacin 400 mg were co-administered, the mean QTcF change from baseline was additive when compared to either drug alone and produced a mean QTcF change of 9 msec from baseline (90% CI: 6,11). The clinical impact of these QT changes is unknown (see **PRECAUTIONS**, Congenital or Acquired QT Prolongation).

Effects on Exercise Treadmill Test in Patients with Coronary Artery Disease (CAD): In two independent trials that assessed 10 mg (n=41) and 20 mg (n=39) vardenafil, respectively, vardenafil did not alter the total treadmill exercise time compared to placebo. The patient population included men aged 40-80 years with stable exercise-induced angina documented by at least one of the following: 1) prior history of MI, CABG, PTCA, or stenting (not within 6 months); 2) positive coronary angiogram showing at least 60% narrowing of the diameter of at least one major coronary artery; or 3) a positive stress echocardiogram or stress nuclear perfusion study.

Results of these studies showed that LEVITRA did not alter the total treadmill exercise time compared to placebo (10 mg LEVITRA vs. placebo: 433±109 and 426±105 seconds, respectively; 20 mg LEVITRA vs. placebo: 414±114 and 411±124 seconds, respectively). The total time to angina was not altered by LEVITRA when compared to placebo (10 mg LEVITRA vs. placebo: 291±123 and 292±110 seconds; 20 mg LEVITRA vs. placebo: 354±137 and 347±143 seconds, respectively). The total time to 1 mm or greater ST-segment depression was similar to placebo in both the 10 mg and the 20 mg LEVITRA groups (10 mg LEVITRA vs. placebo: 380±108 and 334±108 seconds; 20 mg LEVITRA vs. placebo: 364±101 and 366±105 seconds, respectively).

Effects on Vision: Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue test and reductions in electroretinogram (ERG) b-wave amplitudes, with peak effects near the time of peak

plasma levels. These findings are consistent with the inhibition of PDE6 in rods and cones, which is involved in phototransduction in the retina. The findings were most evident one hour after administration, diminishing but still present 6 hours after administration. In a single dose study in 25 normal males, LEVITRA 40 mg, twice the maximum daily recommended dose, did not alter visual acuity, intraocular pressure, fundoscopic and slit lamp findings.

CLINICAL STUDIES

LEVITRA was evaluated in four major double-blind, randomized, placebo-controlled, fixed-dose, parallel design, multicenter trials in 2431 men aged 20-83 (mean age 57 years; 78% White, 7% Black, 2% Asian, 3% Hispanic and 10% Other/Unknown). The doses of LEVITRA in these studies were 5 mg, 10 mg, and 20 mg. Two of these trials were conducted in the general ED population and two in special ED populations (one in patients with diabetes mellitus and one in post-prostatectomy patients). LEVITRA was dosed without regard to meals on an as needed basis in men with erectile dysfunction (ED), many of whom had multiple other medical conditions. The primary endpoints were assessed at 3 months.

Primary efficacy assessment in all four major trials was by means of the Erectile Function (EF) Domain score of the validated International Index of Erectile Function (IIEF) Questionnaire and two questions from the Sexual Encounter Profile (SEP) dealing with the ability to achieve vaginal penetration (SEP2), and the ability to maintain an erection long enough for successful intercourse (SEP3).

In all four fixed-dose efficacy trials, LEVITRA showed clinically meaningful and statistically significant improvement in the EF Domain, SEP2, and SEP3 scores compared to placebo. The mean baseline EF Domain score in these trials was 11.8 (scores range from 0-30 where lower scores represent more severe disease). LEVITRA (5 mg, 10 mg, and 20 mg) was effective in all age categories (<45, 45 to <65, and ≥65 years) and was also effective regardless of race (White, Black, Other).

Trials in a General Erectile Dysfunction Population: In the major North American fixed-dose trial, 762 patients (mean age 57, range 20-83 years; 79% White, 13% Black, 4% Hispanic, 2% Asian and 2% Other) were evaluated. The mean baseline EF Domain scores were 13, 13, 13, 14 for the LEVITRA 5 mg, 10 mg, 20 mg and placebo groups, respectively. There was significant improvement ($p < 0.0001$) at 3 months with LEVITRA (EF Domain scores of 18, 21, 21, for the 5 mg, 10 mg, and 20 mg dose groups, respectively) compared to the placebo group (EF Domain score of 15). The European trial (total N=803) confirmed these results. The improvement in mean score was maintained at all doses at 6 months in the North American trial.

In the North American trial, LEVITRA significantly improved the rates of achieving an erection sufficient for penetration (SEP2) at doses of 5 mg, 10 mg, and 20 mg compared to placebo (65%, 75%, and 80%, respectively, compared to a 52% response in the placebo group at 3 months; $p < 0.0001$). The European trial confirmed these results.

LEVITRA demonstrated a clinically meaningful and statistically significant increase in the overall per-patient rate of maintenance of erection to successful intercourse (SEP3) (51% on 5 mg, 64% on 10 mg, and 65% on 20 mg, respectively, compared to 32% on placebo; $p < 0.0001$) at 3 months in the North American trial. The European trial showed comparable efficacy. This improvement in mean score was maintained at all doses at 6 months in the North American trial.

Trial in Patients with ED and Diabetes Mellitus: LEVITRA demonstrated clinically meaningful and statistically significant improvement in erectile function in a prospective, fixed-dose (10 and 20 mg LEVITRA), double-blind, placebo-controlled trial of patients with diabetes mellitus (n=439; mean age 57 years, range 33-81; 80% White, 9% Black, 8% Hispanic, and 3% Other).