(2)ヨーロッパ第III相試験

	プラセボ	バルデナフィル	
		5mg	10mg
IIEF勃起機能ドメインスコア	N=158	N=150	N=155
投与前 投与後	13.0 13.2±0.6	13.2 19.8±0.6 p<0.0001	13.0 20.9±0.6 p<0.0001
患者日記／「挿入の成功」(%)	N=152	N=152	N=151
投与前 投与後	41.7 45.3±2.6	47.8 71.7±2.6 p<0.0001	43.9 76.4±2.6 p<0.0001
患者日記／「勃起の持続」(%)	N=151	N=152	N=151
投与前 投与後	15.9 24.9±2.9	14.6 54.9±2.9 p<0.0001	15.9 61.6±2.9 p<0.0001

投与前の値は調整済平均値(LS mean)，投与後の値は調整済平均値(LS mean)±SE.
検定は共分散分析を用いたプラセボとの比較.

副作用は，プラセボ群では10.0%(16/160例)，5mg群では19.1%(30/157例)，10mg群では27.7%(44/159例)，20mg群では40.5%(66/163例)に認められた.

■ 薬効薬理

1. 作用機序

陰茎海綿体平滑筋及び関連小動脈を弛緩させて陰茎を勃起させるcGMPは，グアニル酸シクラーゼによる合成とPDE5による加水分解とのバランスにより調節されている．バルデナフィルはPDE5を阻害することによりcGMP量を増加させ，陰茎を勃起させる[35].

2. PDE5阻害作用

バルデナフィルは強力にPDE5を阻害する．ヒト血小板，ヒト陰茎海綿体及び遺伝子組換ヒト型のPDE5に対するIC_{50}値は，それぞれ0.7，3.4及び0.89nMであった(*in vitro*)[35,36].

3. PDE5選択性

バルデナフィルはPDE5を選択的に阻害し，その作用は他のPDEsに対する作用より10～1000倍強い(*in vitro*)[35].(IC_{50}値；PDE5：0.89nM，PDE1：121nM，PDE6：11～157nM，PDE11：308nM，PDE2，PDE3，PDE4，PDE7，PDE8，PDE9及びPDE10に対するIC_{50}値：≧1000nM).

4. 陰茎海綿体中cGMP増加作用

3nM以上の濃度で，NO供与体であるニトロプルシドナトリウム(SNP)1μMによるヒト摘出陰茎海綿体中cGMP濃度増加を濃度依存的に増強した(*in vitro*)[37].

5. 海綿体弛緩増強作用

ヒト摘出陰茎海綿体のSNPによる弛緩に対し，3nM以上で濃度依存的で有意な増強作用を示した(*in vitro*)[37].

6. 陰茎勃起作用

ウサギに1，3，10，30mg/kgを経口投与することにより用量依存的な陰茎勃起作用が認められた．また，性的刺激に代わるものとしてのSNP0.2mg/kg静脈内投与によりバルデナフィルの陰茎勃起作用は著明に増強され，0.1mg/kg以上で用量依存的で，かつ有意な増強作用がみられた[37,38].

■ 有効成分に関する理化学的知見

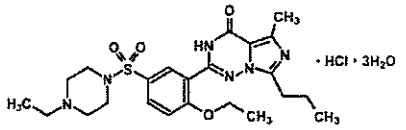
一般名：塩酸バルデナフィル水和物
(Vardenafil Hydrochloride Hydrate) JAN
(Vardenafil INN)

化学名：1-[[3-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethylpiperazine monohydrochloride trihydrate

分子式：$C_{23}H_{32}N_6O_4S \cdot HCl \cdot 3H_2O$

分子量：579.11

構造式：



性　状：塩酸バルデナフィル水和物は白色～微黄色の結晶性の粉末である.
本品はエタノール(99.5)又は水にやや溶けやすい.

■ 包　装

錠　剤
5mg PTP包装　20錠(4錠×5)
10mg PTP包装　20錠(4錠×5)，40錠(4錠×10)
**20mg PTP包装　20錠(4錠×5)，40錠(4錠×10)

■ 主要文献

1) Rajagopalan, P. et al.：バイエル薬品社内資料
2) Lettieri, J. et al.：バイエル薬品社内資料
3) Bauer, R. J. et al.：バイエル薬品社内資料
4) Spera, P. A. et al.：バイエル薬品社内資料
5) Spera, P. A. et al.：バイエル薬品社内資料
6) Mazzu, A. L. et al.：バイエル薬品社内資料
7) Morganroth, J. et al.：*Am. J. Cardiol.*, **93**(11), 1378(2004)
8) Ruf, T. et al.：バイエル薬品社内資料
** 9) Gilad, R. et al.：*Br. Med. J.*, **325**(7369), 869(2002)
** 10) Striano, P. et al.：*Br. Med. J.*, **333**(7572), 785(2006)
11) 香月正憲：バイエル薬品社内資料
12) Bauer, R. J. et al.：バイエル薬品社内資料
13) Hollister, A. et al.：バイエル薬品社内資料
14) Rohde, G. et al.：バイエル薬品社内資料
15) Radtke, M. et al.：バイエル薬品社内資料
16) Witt-Laido, A. et al.：バイエル薬品社内資料
17) Kohlsdorfer, C. et al.：バイエル薬品社内資料
18) Rajagopalan, P. et al.：*J. Clin. Pharmacol.*, **43**(3), 260(2003)
19) Hollister, A. et al.：バイエル薬品社内資料
20) Rohde, G. et al.：バイエル薬品社内資料
21) Rajagopalan, P. et al.：バイエル薬品社内資料
22) Bauer, R. J. et al.：バイエル薬品社内資料
23) Bauer, R. J. et al.：バイエル薬品社内資料
24) Bauer, R. J. et al.：バイエル薬品社内資料
25) Rohde, G. et al.：バイエル薬品社内資料
26) Bauer, R. J. et al.：バイエル薬品社内資料
27) Rohde, G. et al.：バイエル薬品社内資料
28) Rajagopalan, P. et al.：バイエル薬品社内資料
29) Bauer, R. J. et al.：バイエル薬品社内資料
30) Nagao, K. et al.：*Int. J. Urology*, **11**(7), 515(2004)
** 31) Ishii, N. et al.：*Int. J. Urology*, **13**(8), 1066(2006)
** 32) Kimoto, Y. et al.：*Int. J. Urology*, **13**(11), 1428(2006)
33) Hellstrom, W. J. et al.：*J. Androl.*, **23**(6), 763(2002)
34) Collins, O. et al.：バイエル薬品社内資料
35) Bischoff, E. et al.：バイエル薬品社内資料
36) Bischoff, E. et al.：バイエル薬品社内資料
37) Saenz de Tejada, I. et al.：*Int. J. Impotence Res.*, **13**(5), 282(2001)
38) Bischoff, E. et al.：*J. Urol.*, **165**, 1316(2001)

■ 文献請求先

バイエル薬品株式会社・学術情報
〒532-8577 大阪市淀川区宮原三丁目5番36号

■ バイエル医療用医薬品のお問い合わせ先

バイエル薬品株式会社・くすり相談　0120-106-398

製造販売元 バイエル薬品株式会社
大阪市淀川区宮原三丁目5番36号

要望書

平成19年 4月 18日

厚生労働大臣　柳沢 伯夫 殿
厚生労働省医薬食品局安全対策課 課長　伏見 環 殿

拝啓

時下、益々ご清栄のこととお慶び申し上げます。

この度、日本性機能学会は、以下に記載いたしました理由から、レビトラ錠の添付文書改訂を要望いたします。宜しくご検討頂きますようお願い申し上げます。

敬具

記

1. 薬品名：バルデナフィル
2. 要望事項：現行の添付文書における禁忌から「α遮断薬を投与中の患者」を削除し、使用上の注意－1.慎重投与の項に加えることを検討する
3. 背景及び要望理由：

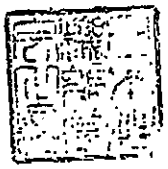
PDE5阻害剤は経口投与可能な勃起障害治療薬として、本邦では1999年にシルデナフィルが上市され、その後2004年にバルデナフィルが上市されている。先に上市されたシルデナフィルはα遮断薬との併用が「慎重投与」とされているが、バルデナフィルではその併用は「禁忌」とされている。後者の設定に際しては、米国における承認当初、FDAが当該併用例の安全性情報が十分でないと判断し、「禁忌」としたことが影響していると思われる。しかし、その後米国における添付文書では「慎重投与」へと改訂されている。また、欧州各国では承認当初より「慎重投与」扱いである。

本邦で実施されたシルデナフィルの臨床試験（西日本泌尿器科 62(6): 373-382, 2000）によると、投与12週後の有効率は72.4%であり、約30%の無効例が存在することが示された。シルデナフィル無効例のみを対象としたバルデナフィルの国外臨床試験（BJU Int. 94(9): 1301-1309, 2004）では、半数以上で有効であったことから、このような難治例に対しては、バルデナフィルへの切り替えを検討すべきと考えられる。しかしながら、本邦の添付文書に従えば、その対象はα遮断薬非併用例に限定されるため、前立腺肥大症などの合併症のためα遮断薬を併用することが多いこれら患者の多くは適用外となる。

2 剤目のバルデナフィルにおいても、国内外で多くの臨床データが集積された現時点では、α遮断薬との併用の取り扱いに関してシルデナフィルと差があるのは不自然であり、本邦においても科学的根拠に基づいて添付文書の見直しを早急に実施することを要望いたします。

以上

日本性機能学会 理事長
東邦大学医学部泌尿器科学講座
教授 石井 延久



1. NAME OF THE MEDICINAL PRODUCT

LEVITRA 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg vardenafil (as hydrochloride trihydrate)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Orange round tablets marked with the BAYER-cross on one side and 5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

LEVITRA is not indicated for use by women.

4.2 Posology and method of administration

Oral use.

Adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. LEVITRA can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see Section 5.2).

Elderly men

Since vardenafil clearance is reduced in elderly patients (see Section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

Children and adolescents

LEVITRA is not indicated for individuals below 18 years of age.

Use in patients with impaired hepatic function

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B).Based on tolerability and efficacy, the dose may be increased to 10 mg and then 20 mg (see section 5.2).

Use in patients with impaired renal function

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

Use in patients using other medicinal products .

When used in combination with the CYP 3A4 inhibitor erythromycin, the dose of vardenafil should not exceed 5 mg (see Section 4.5).

4.3 Contraindications

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see Section 4.5 and 5.1).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment (Child-Pugh C), endstage renal disease requiring dialysis, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction (within the last 6 months), unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with potent CYP3A4 inhibitors (ritonavir, indinavir, ketoconazole and itraconazole (oral form)) is contraindicated in men older than 75 years.

Hypersensitivity to vardenafil or to any of the excipients.

4.4 Special warnings and special precautions for use

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

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

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

The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of vardenafil with alpha-blockers may lead to symptomatic hypotension in some patients. Until further information is available, the concomitant use of vardenafil and alpha-blockers is not recommended.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided as very high plasma concentrations of vardenafil are reached if the drugs are combined (see Section 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if the CYP 3A4 inhibitors, erythromycin, is given concomitantly (see Section 4.5 and Section 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see Section 4.5).

Vardenafil has not been studied in patients with spinal cord injury or other CNS disease, hypoactive sexual desire and in patients who have undergone pelvic surgery (except nerve-sparing prostatectomy), pelvic trauma or radiotherapy.

In vitro studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicyclic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vardenafil

In vitro studies:

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

In vivo studies:

Co-administration of the HIV protease inhibitor indinavir (800 mg t.i.d.), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level (C_{max}) (see Section 4.4).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max} (see Section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole or ritonavir) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole and indinavir. Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided (see Section 4.4).

Co-administration of erythromycin (500 mg t.i.d.), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max}. When used in combination with erythromycin, vardenafil dose adjustment might be necessary (see Section 4.2 and

Section 4.4). Cimetidine (400 mg b.i.d.), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and C_{max} when co-administered with vardenafil (20 mg) to healthy volunteers.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see Section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H2-antagonist ranitidine (150-mg-b.i.d.), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin).

Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see Section 4.3).No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

4.6 Pregnancy and lactation

LEVITRA is not indicated for use by women.

4.7 Effects on ability to drive and use machines

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to LEVITRA, before driving or operating machinery.

4.8 Undesirable effects

Over 3750 patients have received LEVITRA in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in ≥ 10% of patients are headache and flushing.

The following adverse reactions have been reported in clinical trials:

Body System	Very Common (≥ 10%)	Common (>1% < 10%)	Uncommon (> 0.1% < 1%)*	Rare (> 0.01% < 0.1%)*
Digestive		Dyspepsia Nausea		
Nervous System		Dizziness		Hypertonia
Cardiovascular	Flushing		Hypertension	Hypotension *Syncope*
Respiratory		Rhinitis		
Body as a Whole	Headache		Photosensitivity reaction	
Special senses			Abnormal vision	
Urogenital				Erectile disturbance

*For adverse reactions reported in <1% of patients, only those which warrant special attention, because of their possible association with serious disease states or of otherwise clinical relevance, and which have been reported in >2 cases are listed.

In addition, two cases of priapism have been observed in a Phase I clinical study with 40 mg vardenafil (twice the maximum recommended dose).

In a study evaluating visual function with twice the maximum recommended dose of vardenafil, some patients were found to have mild and transient impairment of colour discrimination in the blue/green range and in the purple range one hour after dosing. These changes had improved by six hours and no changes were present at 24 hours. The majority of these patients had no subjective visual symptoms.

Serious cardiovascular events, including cerebrovascular haemorrhage, myocardial infarction, sudden cardiac death, transient ischeamic attack and ventricular arrhythmia have been reported post marketing in temporal association with another medicinal product in this class.

4.9 Overdose

In single dose volunteer studies, doses up to and including 80 mg per day were tolerated without exhibiting serious adverse reactions.

When vardenafil was administered in higher doses and more frequently than the recommended dosing regimen (40 mg b.i.d.) cases of severe back pain have been reported. This was not associated with any muscle or neurological toxicity.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance, as vardenafil is highly bound to plasma proteins and not significantly eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal product used in erectile dysfunction, ATC code: G04B E09

Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e. with sexual stimulation it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation, allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

In vitro studies have shown that vardenafil is more potent on PDE5 than on other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plesthysmography (RigiScan) study, vardenafil 20 mg produced erections considered *sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing.* The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

Vardenafil causes mild and transient decreases in blood pressure which, in the majority of the cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 20 mg and 40 mg vardenafil were – 6.9 mmHg under 20 mg and – 4.3 mmHg under 40 mg *of vardenafil, when compared to placebo. These effects are consistent with the vasodilatory effects of* PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Further information on clinical trials

In clinical studies vardenafil was administered to over 3750 men with erectile dysfunction (ED) aged 18 - 89 years, many of whom had multiple co-morbid conditions. Over 1630 patients have been treated with LEVITRA for six months or longer. Of these, over 730 have been treated for one year or longer. The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidaemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see Section 4.3). No clinical studies in spinal cord injury or other CNS diseases, patients with severe renal or hepatic impairment, pelvic surgery (except nerve-sparing prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad

ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

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 C_{max} 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

1. NAME OF THE MEDICINAL PRODUCT

LEVITRA 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg vardenafil (as hydrochloride trihydrate)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Orange round tablets marked with the BAYER-cross on one side and 10 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

LEVITRA is not indicated for use by women.

4.2 Posology and method of administration

Oral use.

Adult men

The recommended dose is 10 mg taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to 20 mg or decreased to 5 mg. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. LEVITRA can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal (see Section 5.2).

Elderly men

Since vardenafil clearance is reduced in elderly patients (see Section 5.2) a first dose of 5 mg should be used. Based on efficacy and tolerability the dose may be increased to 10 mg and 20 mg.

Children and adolescents

LEVITRA is not indicated for individuals below 18 years of age.

Use in patients with impaired hepatic function

A starting dose of 5 mg should be considered in patients with mild and moderate hepatic impairment (Child-Pugh A-B).Based on tolerability and efficacy, the dose may be increased to 10 mg and then 20 mg (see section 5.2).

Use in patients with impaired renal function

No dosage adjustment is required in patients with mild to moderate renal impairment.

In patients with severe renal impairment (creatinine clearance < 30 ml/min), a starting dose of 5 mg should be considered. Based on tolerability and efficacy the dose may be increased to 10 mg and 20 mg.

Use in patients using other medicinal products

When used in combination with the CYP 3A4 inhibitor erythromycin, the dose of vardenafil should not exceed 5 mg (see Section 4.5).

4.3 Contraindications

The coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see Section 4.5 and 5.1).

Agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure [New York Heart Association III or IV]).

The safety of vardenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment (Child-Pugh C), endstage renal disease requiring dialysis, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction (within the last 6 months), unstable angina and known hereditary retinal degenerative disorders such as retinitis pigmentosa.

Concomitant use of vardenafil with potent CYP3A4 inhibitors (ritonavir, indinavir, ketoconazole and itraconazole (oral form)) is contraindicated in men older than 75 years.

Hypersensitivity to vardenafil or to any of the excipients.

4.4 Special warnings and special precautions for use

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

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

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

The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

The concomitant use of vardenafil with alpha-blockers may lead to symptomatic hypotension in some patients. Until further information is available, the concomitant use of vardenafil and alpha-blockers is not recommended.

Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided as very high plasma concentrations of vardenafil are reached if the drugs are combined (see Section 4.5 and 4.3).

Vardenafil dose adjustment might be necessary if the CYP 3A4 inhibitors, erythromycin, is given concomitantly (see Section 4.5 and Section 4.2).

Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided (see Section 4.5).

Vardenafil has not been studied in patients with spinal cord injury or other CNS disease, hypoactive sexual desire and in patients who have undergone pelvic surgery (except nerve-sparing prostatectomy), pelvic trauma or radiotherapy.

In vitro studies with human platelets indicate that vardenafil has no antiaggregatory effect on its own, but at high (super-therapeutic) concentrations vardenafil potentiates the antiaggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, vardenafil had no effect on bleeding time alone or in combination with acetylsalicyclic acid (see section 4.5). There is no safety information available on the administration of vardenafil to patients with bleeding disorders or active peptic ulceration. Therefore vardenafil should be administered to these patients only after careful benefit-risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on vardenafil

In vitro studies:

Vardenafil is metabolised predominantly by hepatic enzymes via cytochrome P450 (CYP) isoform 3A4, with some contribution from CYP3A5 and CYP2C isoforms. Therefore, inhibitors of these isoenzymes may reduce vardenafil clearance.

In vivo studies:

Co-administration of the HIV protease inhibitor indinavir (800 mg t.i.d.), a potent CYP3A4 inhibitor, with vardenafil (10 mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}. At 24 hours, the plasma levels of vardenafil had fallen to approximately 4% of the maximum vardenafil plasma level (C_{max}) (see Section 4.4).

Co-administration of ketoconazole (200 mg), a potent CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max} (see Section 4.4).

Although specific interaction studies have not been conducted, the concomitant use of other potent CYP3A4 inhibitors (such as itraconazole or ritonavir) can be expected to produce vardenafil plasma levels comparable to those produced by ketoconazole and indinavir. Concomitant use of vardenafil with potent CYP 3A4 inhibitors (ritonavir, indinavir, itraconazole and ketoconazole (oral form)) should be avoided (see Section 4.4).

Co-administration of erythromycin (500 mg t.i.d.), a CYP3A4 inhibitor, with vardenafil (5 mg) resulted in a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max}. When used in combination with erythromycin, vardenafil dose adjustment might be necessary (see Section 4.2 and Section 4.4). Cimetidine (400 mg b.i.d.), a non-specific cytochrome P450 inhibitor, had no effect on vardenafil AUC and C_{max} when co-administered with vardenafil (20 mg) to healthy volunteers.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil (see Section 4.4).

The pharmacokinetics of vardenafil (20 mg) was not affected by co-administration with the H2-antagonist ranitidine (150-mg-b.i.d.), digoxin, warfarin, glibenclamide, alcohol (mean maximum blood alcohol level of 73 mg/dl) or single doses of antacid (magnesium hydroxide/aluminium hydroxide).

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect on vardenafil pharmacokinetics of the following concomitant medicinal products: acetylsalicylic acid, ACE-inhibitors, beta-blockers, weak CYP 3A4 inhibitors, diuretics and medications for the treatment of diabetes (sulfonylureas and metformin).

Effects of vardenafil on other medicinal products

There are no data on the interaction of vardenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

In vivo studies:
No potentiation of the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) was observed when vardenafil (10 mg) was given at varying time intervals (1 h to 24 h) prior to the dose of nitroglycerin in a study in 18 healthy male subjects. However, there is no information on the possible potentiation of the hypotensive effects of nitrates by vardenafil in patients, and concomitant use is therefore contraindicated (see Section 4.3).No significant interactions were shown when warfarin (25 mg), which is metabolised by CYP2C9, or digoxin (0.375 mg) was co-administered with vardenafil (20 mg). The relative bioavailability of glibenclamide (3.5 mg) was not affected when co-administered with vardenafil (20 mg). In a specific study, where vardenafil (20 mg) was co-administered with slow release nifedipine (30 mg or 60 mg) in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 6 mmHg and supine diastolic blood pressure of 5 mmHg accompanied with an increase in heart rate of 4 bpm.

When vardenafil (20 mg) and alcohol (mean maximum blood alcohol level of 73 mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered.

Vardenafil (10 mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid (2 x 81 mg).

4.6 Pregnancy and lactation

LEVITRA is not indicated for use by women.

4.7 Effects on ability to drive and use machines

As dizziness and abnormal vision have been reported in clinical trials with vardenafil, patients should be aware of how they react to LEVITRA, before driving or operating machinery.

4.8 Undesirable effects

Over 3750 patients have received LEVITRA in clinical trials. The adverse reactions were generally transient and mild to moderate in nature. The most commonly reported adverse drug reactions occurring in ≥ 10% of patients are headache and flushing.

The following adverse reactions have been reported in clinical trials: