

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of VIAGRA. This scientific discussion has been updated until 1 December 2002. For information on changes after this date please refer to module 8B.

1. Introduction

Male erectile dysfunction (ED) has been defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance as part of the overall process of male sexual function (NIH Consensus Conference, 1993). ED can have a profound impact on the quality of life with subjects often reporting increased anxiety, loss of self-esteem, lack of self-confidence, tension and difficulty in the relationship with their partner. The prevalence of ED has been found to be associated with age. Complete ED has an estimated prevalence of about 5% in men aged 40 years to 15% at age 70 years. It should be recognised that desire, orgasmic capacity and ejaculatory capacity may be intact even in the presence of erectile dysfunction or may be deficient to some extent and contribute to the sense of inadequate sexual function. The term impotence, together with its pejorative implications, is less precise and should not be used. The degree of erectile dysfunction can vary and may range from a partial decrease in penile rigidity to complete erectile failure and the frequency of these failures may also range from “a few times a year” to “usually unable to obtain an erection”.

ED is often multifactorial in etiology (organic, psychogenic, or mixed). Sometimes ED is related to stress problems with the sexual partner or transient psychological factors.

Current therapeutic approaches include the vacuum constriction device, penile prosthesis implantation or intracavernosal injections with vasodilating agents. They are far from satisfactory for most patients and some of these have limitations to their use.

Recent insights into the mechanism of penile erection have led to the development of sildenafil, a novel orally active drug for the treatment of penile erectile dysfunction. Sildenafil is a new chemical entity and a potent inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

2. Overview of Module III of the dossier: chemical and pharmaceutical aspects

VIAGRA is presented as blue film-coated, rounded diamond shaped tablets containing sildenafil citrate equivalent respectively to 25, 50 and 100 mg of sildenafil. Other components of the tablet core are microcrystalline cellulose and calcium hydrogen phosphate (anhydrous) as diluents, croscarmellose sodium as disintegrant and magnesium stearate as lubricant. A two-stage tablet coating employs an aqueous suspension of Opadry Blue (hypromellose, lactose, triacetin, titanium dioxide and indigo carmine aluminium lake) followed by a protective clear coat of Opadry Clear (hypromellose and triacetin). Two types of standard primary packaging materials were proposed: PVC/PE/ACLAR-Aluminium blister (1 or 4 tablets per blister; cartons containing 1, 4, 8, or 12 tablets) and white opaque high density polyethylene (HDPE) bottles (4, 8 or 12 per bottle) with child-resistant closures with external polypropylene internal polyethylene sealing. A final decision was taken by the applicant to only market blister packs and therefore, the bottle presentations were withdrawn (27 May 98).

Active substance

Sildenafil citrate is a white to off-white crystalline powder with a solubility profile dependent on pH. In the solid state, sildenafil citrate is considered to be extremely stable as demonstrated by data derived from forced degradation studies. It is stable at 90°C in an inert atmosphere. Significant degradation occurs only under strong oxidising conditions. Some degradation also occurs under exposure to strong light.

Sildenafil citrate is an achiral substance and the evidence of its chemical structure has been adequately confirmed by elemental analysis, IR NMR, and mass spectroscopy and X-ray crystallography. Other

physico-chemical data such as potentiometric titration, UV absorption spectra, dissociation constants, thermal studies, hygroscopicity and solubility studies provide further supportive evidence of chemical structure.

Sildenafil citrate is manufactured in a 3-step synthesis. Purifications have been set up after each step of synthesis. The final solid is separated, washed, dried, and then sieved or milled to meet the particle size specification.

Stringent specifications have been set for the synthesis starting materials and intermediates and are considered to be adequate. Extensive validation data and chromatograms confirm the quality of the starting materials. The specifications for solvents and reagents are also considered to be satisfactory for such materials.

The assay of sildenafil citrate and specified impurities are determined by HPLC. The level of solvent, used during the purification and crystallisation phases of the sildenafil citrate, is detected within an acceptable limit by a GC method. The impurity limits proposed in the active substance specification have been justified on the basis of toxicology studies and batch analysis data indicate suitable uniformity.

Overall, the active substance is well specified and characterised. Limits are acceptable in view of batch analysis data and toxicology studies. All analytical methods for starting materials and intermediates have been adequately validated.

The active substance tested, in solid state and in dissolution, under accelerated conditions, show that sildenafil citrate is stable. Stability studies carried out up to 1 year indicate no significant differences in appearance and no formation of degradation products, and support the proposed re-test period of 2 years for the active substance in double polyethylene bags inside a fibre drum.

Finished product

Different formulations were developed and used early in clinical studies (capsule, plain white tablet, plain blue film-coated tablet). As the blue coating was insufficiently robust to take the stresses of full-scale manufacture and shipment, a clear film overcoating was added to the proposed commercial tablet. Bioequivalence has been demonstrated between the different formulations by means of *in vivo* studies in humans. Comparison of the dissolution profiles of the formulation with and without the clear overcoating indicates similar dissolution profiles in a variety of dissolution media.

Pharmaceutical development

The tablets are manufactured using a conventional tablet formulation, conventional pharmaceutical equipment and processes. Development of the formulation and the manufacturing processes (roller compaction, compression and film-coating) are well described. Compatibility studies demonstrated that sildenafil citrate was stable with all the tablet excipients except magnesium stearate, which causes degradation with sildenafil in binary mixtures under stress conditions. However, further stability studies showed no degradation and magnesium stearate was subsequently selected as lubricant.

Manufacture and control

The manufacturing process consists of blending, screening, lubrication, roller compaction, and compression. The tablet cores are first coated with a blue Opadry coating, and then a clear overcoat. Adequate in-process controls are provided to ensure tablet quality. Prior to compression, the potency and uniformity of the lubricated blend are determined by specific HPLC assay.

The tablet excipients including the coating components (except for triacetin and indigo carmine aluminium lake) comply with Ph. Eur, and analytical certificates provided are acceptable. Triacetin and indigo carmine aluminium lake are specified to USP and Ph. Fr., respectively.

Batches have been manufactured to 100% industrial scale (360 kg). Batches obtained from different manufacturing sites were of homogeneous characteristics. Furthermore, analytical results of the blend and the tablets without (17 batches) or with clear overcoating (5 batches), manufactured from different sites, indicates that the manufacturing technology has been successfully transferred to the commercial production facility. The manufacturing process is identically robust for the three tested sites and has been adequately validated for the commercial formulation at the intended production scale.

Product specification

Control tests on the finished product use adequately validated methods, including requirements for appearance, visual identification, identification and quantitative determination of active substance, determination of degradation products, uniformity of mass, water content and dissolution testing. The specification limit for total degradation products (shelf life) is 0.2% maximum. The microbiological quality is controlled in accordance with Ph. Eur., but is proposed as a non-routine method. Therefore the microbiological quality of the product should be controlled at the end of its re-test period.

Results from batch analyses showed that all batches complied with release specifications and demonstrated acceptable batch to batch consistency.

Stability

For the finished product stored in the proposed packaging materials, long-term stability studies have been carried out at different temperatures and conditions (25°C/60%RH, 30°C/60%RH, 40°C/75%RH) on batches resulting from Brooklyn (clear coated) up to 9 months, from Amboise (clear coated) up to 6 months and up to 12 months (non clear coated). Based on the resulting data, a 2-years shelf life is acceptable when the product is stored below 30°C.

In summary, sildenafil film-coated tablets 25, 50 and 100 mg are conventionally formulated and manufactured using standard pharmaceutical technology. The chemical-pharmaceutical dossier is well documented and guarantees the quality of the active substance and the finished product with regard to uniform efficacy and safety. The specifications set are suitable. The company was however requested to provide, within the agreed timeframe, batch analysis data generated from full-scale production batches, and additional supportive stability data to confirm the 2-year shelf-life. The data provided substantiate the stability of the finished product over a maximum of 5 years.

3. Overview of Module IV of the dossier: toxico-pharmacological aspects

Pharmacodynamics

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific PDE5 in the corpus cavernosum, and hence inhibits the degradation of cGMP without affecting cyclic AMP (cAMP). Studies examining mechanisms of penile erection have demonstrated that during sexual stimulation, nitric oxide (NO) is released from penile nerve endings. This acts to increase levels of cGMP in the corpus cavernosum smooth muscle which is responsible for the vascular events leading to erection. PDE5, which is abundantly present in the corpus cavernosum, breaks down cGMP levels generated under sexual stimulation. Sildenafil, by inhibiting PDE5, prevents this breakdown and thus enhances the induced erectile response. PDE inhibitors do not stimulate the production of cyclic nucleotides, thus tissue cGMP levels will only increase following physiological activation of guanylate cyclase.

Over 70 *in vitro* and *in vivo* pharmacodynamic studies have been conducted to demonstrate the selectivity and potency of sildenafil and its main circulating metabolite in animals. The pharmacodynamic evaluation demonstrates the functional effects of sildenafil in the target tissue as a consequence of PDE5 inhibition and also investigates its effect in tissues other than the corpus cavernosum, especially effects on platelets, smooth muscles (PDE5) and the retina (PDE6).

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3. The cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility is of particular importance given the known cardiovascular activity of PDE3 inhibitors.

In radio-ligand binding studies sildenafil displayed little affinity for α_1 -, α_2 -, and β -adrenergic receptors, dopamine (D₁ and D₂), histamine (H₁), 5-HT₁, 5-HT₂, muscarinic and opioid receptors and dihydropyridine, verapamil, diltiazem, and benzodiazepine binding sites.

Effects on corpus cavernosum: In phenylephrine (PE) precontracted isolated rabbit and human corpus cavernosum strips, sildenafil enhanced the relaxation induced by Electrical Field Stimulation (EFS). Relaxation was inhibited by the NO-synthase inhibitor in both the human and rabbit tissues, and in the rabbit strips by the guanylate cyclase inhibitor methylene blue, L-n-nitroarginine confirming that the NO/cGMP pathway is involved in the relaxation. In the rabbit model sildenafil potentiated the relaxation of the NO donor SNP (sodium nitroprusside) and the endothelium-dependent relaxation of the muscarinic agonist methacholine. In human isolated corpus cavernosum strips, sildenafil in the absence of EFS, had no direct relaxant effects. This may reflect a higher endogenous production of NO in rabbit compared with human isolated corpus cavernosum.

In anaesthetised dogs, sildenafil enhanced the rise in intracavernosal pressure in response to stimulation of the pelvic nerve. L-n-nitroarginine caused a dose related reduction in pressure in this model, demonstrating that sildenafil enhances the NO mediated rise in corpus cavernosum pressure.

Effects on platelet function: Sildenafil had no effect per se on platelet aggregation induced by a range of aggregatory agents, but consistent with inhibition of PDE5, sildenafil potentiated the antiaggregatory and disaggregatory actions of SNP both *in vitro* and *ex vivo*. The consequences of this antiplatelet action have been investigated. There was a trend to increased bleeding time in rat (60% increase not statistically significant, after 0.3 mg/kg i.v.) and bleeding time prolongation was seen in rabbits (129% increase for a dose of 1 mg/kg i.v.). These doses are equivalent to 18.5-25 and 61.7-83.6 times, respectively, the effective dose on corpus cavernosum pressure in anaesthetised dogs.

Haemodynamic activity: Several studies have been conducted to study the haemodynamic activity of sildenafil in different animal species (rabbit, dog, rat, cat). These studies have demonstrated that sildenafil has vasodilator properties which can, at higher doses, be associated with reductions in blood pressure and accompanied by an indirect increase in heart rate. These pharmacological properties are consistent with facial flushing and headache reported as adverse events in clinical studies. However, the submitted data did not show consistent or dose-related systemic haemodynamic effects of sildenafil at plasma concentrations up to 25-fold higher than those active on the corpus cavernosum.

Effects on gastrointestinal smooth muscle: Because PDE5 and PDE1 are expressed in smooth muscle, the effects of inhibiting these PDE isoenzymes in gastrointestinal smooth muscle have been investigated. In several *in vitro* experimental models (rat ileum and oesophageal smooth muscle, mouse ileum, and dog lower oesophageal sphincter) sildenafil at high concentrations reduced gastrointestinal smooth muscle contractility, which may indicate a risk for inhibition of gastric emptying. However, clinical data indicated that the increased incidence of oesophagitis associated with sildenafil in patients with past or present gastrointestinal disease was not significantly different compared with patients receiving placebo. Taken also into consideration the intermittent use of sildenafil, relevant gastrointestinal side effects are not expected.

Effects on the retina: Sildenafil inhibits PDE6 in retina tissue. After absorption of light, rhodopsin stimulates PDE6 via the G-protein transducin. This results in a decrease of the concentration of cGMP leading to hyperpolarisation of the photoreceptors. Studies of the effect of sildenafil on hyperpolarisation *in vitro* and on the electroretinogram (ERG) *in vivo* were conducted in dogs. Sildenafil had an effect *in vitro* on the response of the dog isolated retina to a blue light challenge and changed the ERG in anaesthetised dogs. These effects were observed at plasma concentrations approximately 25 times higher than those active on the corpus cavernosum in anaesthetised dogs.

General pharmacodynamic studies have been carried out in the mouse, rat and cat. In general, sildenafil caused short-lasting falls in blood pressure and left systolic pressure at high doses accompanied by (reflex) increases in heart rate. There was no evidence of a direct effect on the electrical conductance in the heart.

From the studies in isolated gastrointestinal smooth muscle, it is clear that high concentrations of sildenafil can reduce gastrointestinal smooth muscle contractility most likely via the potentiation of the effects of NO. In rats at doses up to 10 mg/kg p.o. sildenafil was without an effect on gastrointestinal propulsive activity or gastric acid secretion. However, in mice, intestinal transit was markedly slowed after single and repeated oral doses of 10 mg/kg and higher. In addition all doses caused an increase in the total length of the small intestine. In rats at doses 10 times higher than those in mice similar effects were observed.

Pharmacodynamic profile of the main sildenafil metabolite: The main circulating metabolite of sildenafil is a slightly weaker inhibitor of PDE5 with an overall selectivity profile similar to that of sildenafil. In anaesthetised rats and dogs, the metabolite caused a dose-related, but transient, fall in mean arterial blood pressure and an increase in heart rate. These changes caused by the metabolite were similar to those caused by the parent compound.

Pharmacokinetics

The pharmacokinetic profile of sildenafil was studied in the mouse, rat, rabbit and dog, the main species used in the preclinical programme. Oral absorption was rapid in all species studied, with T_{max} of 3 hours or less. Systemic bioavailability was attenuated by pre-systemic hepatic metabolism, which is consistent to some extent with the plasma clearance value in each species. This results in higher oral bioavailability in dog (54%) and female rat (44%), compared with male rat (15%) and mouse (17%). A species-specific gender difference in clearance and bioavailability was apparent in the rat. In humans the oral bioavailability is approximately 40%.

Volume of distribution is similar in rodents and humans but is higher in the dog, probably reflecting the lower protein binding in this species. The pattern of tissue distribution with drug-derived radioactivity in rat is that expected for a lipophilic weak base, with radioactivity detectable in most tissues shortly (0.1 hours) after dosing at concentrations generally higher than those in blood. By 24 hours post-dose residual radioactivity was mainly limited to the retina, substantia nigra and the pigmented skin, suggesting that sildenafil and/or its metabolites have an affinity for melanin.

In all species studied, sildenafil is metabolised extensively, resulting in metabolic profiles similar to that observed in man. No significant human-specific metabolites were identified. Clearance of sildenafil is via 5 principal pathways of oxidative metabolism, the majority of the dose being excreted in the faeces over 48 hours. Des-methylation at the N-methyl piperazine moiety yields UK-103,320 as a primary metabolite, and this was present in plasma and excreta from all species studied. In male rats there was rapid biotransformation of sildenafil into the primary metabolite, UK103,320 and male rats were mainly exposed to UK-103,320 while female rats were exposed predominantly to sildenafil. The dog had the longest elimination half-life (5.2 h) and was the closest to that of man (approximately 4 h). In all species the predominant route of excretion was the faeces, which accounted for 73-88% of the dose, in comparison with 6-15% for urine.

Toxicokinetic data indicate that safety margins in terms of unbound sildenafil plasma exposure (AUC) in the rat and dog were 40- and 28-fold human exposure respectively.

Toxicology

Single dose toxicity of sildenafil after oral administration was studied in rodents. Lethality occurred at 1000 mg/kg and 500 mg/kg in rats and 1000 mg/kg in mice. Clinical signs, which preceded mortality, were partially closed eyes, hunched posture, tremors and depression.

Repeated dose toxicity of sildenafil after oral administration was studied in mice (up to 3 months), rat (up to 6 months) and dog (up to 12 months). In repeated dose studies in rat and dog, doses were limited by isolated deaths at 200 mg/kg in rats and by gastric intolerance in dogs at 80 mg/kg. There was no evidence of long term toxicity to the retina. The main effects in rat were adaptive liver changes (associated with thyroid follicular hypertrophy). In dog, heart rate was moderately increased in all studies, with no consistent changes in blood pressure. In chronic dog studies, 50 mg/kg was associated with Idiopathic Juvenile Arteritis, a syndrome thought to be an expression of latent disease precipitated by stress, rather than a direct toxic effect of the compound. No adverse effect levels in the rat and dog were 60 mg/kg and 15 mg/kg respectively. Toxicity to reproduction was studied in rats and rabbits. Overall, sildenafil had no adverse effects on fertility and has no teratogenic potential.

Sildenafil did not induce mutations in bacterial or mammalian cells *in vitro*, nor did it cause clastogenic activity *in vitro* or *in vivo*.

There was no evidence of a carcinogenic effect in mice or rats. In mice (two carcinogenicity studies), mortality was often associated with gastro-intestinal dilatation appearing a few days before death. There was no evidence of alteration to the tumour profile. Investigative studies have shown that the mouse is particularly sensitive to the effects of sildenafil on the gastrointestinal tract. In the rat carcinogenicity study, an increased incidence of proliferative changes in the thyroid in high dose

males was observed, related to an increase in follicular hyperplasia. There was no difference in the incidence of carcinomas. An investigative study suggests that this reflects the enzyme inducing properties of sildenafil, associated with an increased turnover of thyroid hormones, and continuous stimulation of the thyroid by compensatory sustained levels of thyroid stimulating hormone. In the absence of increases in liver weight and of hepatic centrilobular hypertrophy, it was considered that this mechanism probably operates chronically at low level, where liver changes would remain undetectable.

Sildenafil showed no arterial irritancy or antigenicity. An assessment of environmental risk was not performed, and no significant environmental effects are anticipated.

Summary and conclusion on preclinical pharmacology and toxicology:

Overall, the preclinical pharmacodynamic studies have shown that sildenafil has a high potency and selectivity for PDE5 and that via smooth muscle relaxation, sildenafil can induce a rise in intracavernosal pressure during stimulation. Based on this pharmacodynamic profile, several adverse events can be anticipated with the use of sildenafil (such as facial flushing, headache, effect on visual function). However it should be noted that almost all of the possible adverse effects only occur at doses or plasma concentrations far higher than those needed for the intended pharmacodynamic effect of sildenafil.

Pharmacokinetics and toxicokinetics were adequately studied and toxicity was tested appropriately. Sildenafil was well tolerated at relevant dose levels. Toxicokinetic data for both sildenafil and for the main metabolite (UK-103,320) indicate a large margin between plasma exposure to drug-related components in man and that associated with toxicity in rat and dog. Preclinical data revealed no special risk for human. This information has been included in the Summary of Products Characteristics.

4. Overview of Module 5 of the dossier: clinical aspects

The core clinical program, consisting of 31 Phase II/III clinical studies (4 main and other supportive) was aimed at evaluating the efficacy and safety of sildenafil for the treatment of erectile dysfunction (ED) in a broad-spectrum population. In addition, a total of 39 Phase I clinical pharmacology studies have been submitted evaluating safety/tolerability, pharmacodynamics and pharmacokinetics of sildenafil. Studies have been performed in accordance with GCP standards.

Human pharmacology

During sexual stimulation, nitric oxide (NO) is released from penile nerve endings leading to increased levels of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum smooth muscle. cGMP acts as a mediator of vasodilatation. With the relaxation of corporal smooth muscle, arterial filling begins, which initiates the hemodynamic event of a natural erection by engorgement of the sinusoids in the cavernosa and veno-occlusion due to the compression of the subintimal venules against the tunica albuginea. Phosphodiesterase 5 (PDE5), present in the corpus cavernosum, breaks down cGMP. Sildenafil is an inhibitor of the effects of PDE with selectivity and potency on PDE5.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, The cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility is of particular importance given the known cardiovascular activity of PDE3 inhibitors.

Pharmacodynamics

Single oral sildenafil doses larger than 30 mg were associated with increased plasma cGMP levels. The pharmacodynamic effects of sildenafil in subjects with ED of broad-spectrum etiology have been evaluated in response to visual sexual stimulation and tactile stimulation, following doses of 10, 25, 50 and 100 mg, using penile plethysmography as an objective measure of penile rigidity (rigidity > 60% at the base of the penis). Although the number of responders increased with dosing, no clear dose

response relationship was established. Only one study examined time to onset of erection, showing the median time to onset of 27 minutes after 50 mg sildenafil oral dose compared to 50 minutes for the placebo group. In all doses, sildenafil improved the total duration of the erectile response following visual sexual stimulation compared to placebo. The duration of response was wide and ranged, from a mean duration of 22 minutes for plasma sildenafil concentrations in the range 0-50 and 50-100 ng/ml to >30 minutes at concentrations above 100 ng/ml. No correlation was found between time to onset and duration of erections and sildenafil or UK-103,320 plasma concentration.

Sildenafil also demonstrates affinity for PDE6, which is present in the retinal photoreceptors (rods and cones) and plays a key role in phototransduction. Except for increased error scores in color discrimination tests (assessed by means of Farnsworth-Munsell 100 Hue test) reported for sildenafil 100 mg, one hour and two hours post-dose, no specific effects on visual function were seen at the therapeutic dosages. This could be explained by the fact that sildenafil is pharmacologically active on human retinal PDE6 at higher doses than those required for pharmacological activity on the corpus cavernosum. An increase in adverse reactions (abnormal vision, gastrointestinal and cardiovascular) was observed following doses of 200 mg sildenafil.

Mean maximum decreases of 8.4 mmHg in systolic and 5.5 mmHg in diastolic blood pressure, with no effect on heart rate or orthostatic effects, were observed after a single 100 mg oral dose of sildenafil. After a 50 mg dose, there was a mean maximum decrease of 7.7 mmHg in systolic and 4.5 mmHg in diastolic blood pressure. There was a tendency for blood pressure to return to baseline values by 4 hours post-dose.

Vascular studies (venous occlusion plethysmography) showed some veno- and arteriodilator effects on the peripheral vascular system with no clinically significant changes in cardiac index. Sildenafil has no platelet antiaggregatory effect per se at the usual doses. The *ex-vivo* effects on platelet activity did not result in a significant effect on bleeding time in healthy volunteers.

No effect on sperm motility, morphology or vitality at 1.5 and 4 hours post-dose was demonstrated (single dose of 100 mg sildenafil).

No specific studies to investigate the pharmacodynamic effects of sildenafil on the gastrointestinal or central nervous systems have been conducted.

Pharmacokinetics

Absorption - Sildenafil is rapidly absorbed with maximal plasma concentrations occurring about 0.5-2 hours after oral dosing. Absolute bioavailability is about 40% due to the first-pass metabolism (not due to incomplete absorption). Simultaneous intake of food with sildenafil causes a delay in absorption with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution - Approximately 96% of sildenafil was bound to plasma proteins, but its potential for interaction with co-administered drugs due to displacement is limited because of its relatively high volume of distribution, which is about 100 l after i.v. administration of sildenafil. Partitioning of sildenafil and its metabolites into erythrocytes was found *in vivo*. Sildenafil was also distributed into the ejaculate (<0.0002% of the total administered dose).

An increase in AUC and C_{max} of sildenafil was observed with an increase in dose after i.v. (20-80 mg) and oral administration (proportional increase over the dose range of 25-100 mg). At higher doses, no differences were seen in T_{max} .

Metabolism and excretion - Sildenafil is extensively metabolised by hepatic microsomes, involving two cytochrome P450 isoforms (CYP3A4 as the major route and CYP2C9 as a minor route). Four metabolites were detected in plasma: an N-desmethyl-metabolite (UK-103,320), a metabolite formed by loss of a two carbon fragment from the piperazine ring (UK-150,564), an aliphatic-hydroxylate metabolite and an unidentified-metabolite. UK-103,320 and UK-150,564 appeared to be the only metabolites with comparable selectivity but weaker potency than the parent compound (50 and 10%, respectively). Moreover, their plasma concentrations were about 20-40% of those of the parent compound, and therefore a major contribution to the pharmacological effect in man is not expected.

Sildenafil is mainly cleared from the plasma non-renal (clearance around 41 l/h, comparable to hepatic plasma flow), with a mean terminal half-life of approximately 4 hours. No accumulation is

expected when sildenafil is administered once daily. Sildenafil and its main metabolites have mainly a biliary route of excretion (75-80% of radioactivity excreted in faeces).

Interactions - CYP3A4 is indicated as the main isoenzyme involved in sildenafil metabolism; consequently, inhibitors of this isoenzymes may reduce sildenafil clearance. Population pharmacokinetics indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, and cimetidine). Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, showed interaction resulting in an increase of the sildenafil (50 mg) plasma concentrations of approximately 56%. Multiple dosing of erythromycin, to steady state (500 mg b.i.d. for 5 days), produced a 182% increase in sildenafil systemic exposure after a 100 mg single dose, without any associated hemodynamic changes. Data from clinical trials on the incidence of all causality adverse events for subjects on sildenafil and concomitant erythromycin showed no difference to placebo treatment. Given the reduced clearance of sildenafil when co-administrated with a CYP3A4 inhibitor, a starting dose of sildenafil 25 mg should be considered.

Coadministration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg tid) with sildenafil (100 mg single dose) resulted in a 140 % increase in sildenafil C_{max} and a 210 % increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects. Given the reduced clearance of sildenafil when coadministered with HIV protease inhibitors, a starting dose of sildenafil 25mg should be considered.

Coadministration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with sildenafil (100 mg single dose) resulted in a 300 % (4-fold) increase in sildenafil C_{max} and a 1,000 % (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised, and in any event the maximum dose of sildenafil administered to a patient receiving ritonavir should not exceed 25 mg within 48 hours.

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Moreover, because the expected plasma concentrations of sildenafil are less than 1 microM after recommended doses, it is unlikely that sildenafil (or the metabolite UK-103.320) will be associated with these isoenzyme based drug interactions. No pharmacokinetic interaction with tolbutamide (250 mg) and no effect on the dynamic properties of warfarin (40 mg), both of which are metabolised by CYP2C9, were demonstrated when co-administered with sildenafil (50 mg). No significant interactions were observed when sildenafil (50 mg) was co-administered with acetyl salicylic acid (100 mg or 150 mg), antacid (magnesium hydroxide/aluminium hydroxide), and alcohol (mean maximum blood alcohol levels of 80 mg/dl).

There are no data on the interaction of sildenafil with non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole. The company has committed itself, within the agreed timeframe, to conduct *in vitro* interaction studies with these medicinal products. *Ex-vivo* studies with human platelets indicated that sildenafil potentiates the antiaggregatory effects of sodium nitroprusside; these effects did not result in a significant effect on bleeding time in healthy volunteers. However, since there is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration, sildenafil should therefore be administered to these patients only after careful benefit-risk assessment.

Pooling adverse event data for patients on the following concomitant antihypertensive medications: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoreceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction in supine systolic blood pressure of 8 mmHg and the corresponding additional reduction in supine diastolic blood pressure of 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.

Sildenafil potentiated the hypotensive effects of sublingual and intravenous glyceryl trinitrate; therefore its concomitant administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form has been contraindicated in the SPC.

Special populations – Although only a small amount (<4% of dose) of unchanged parent drug is excreted renally, AUC and C_{max} of sildenafil (50 mg) increased significantly by 100% and 88%, respectively, in subjects with severe renal impairment (creatinine clearance <30 ml/min) compared to healthy subjects. In addition, the pharmacokinetics of the active N-desmethyl metabolite were affected by severe renal dysfunction, resulting in a significant increases in AUC and C_{max} of about 79% and 200% respectively. A greater decrease in blood pressure was detected in the renally impaired subjects compared to healthy subjects. In the clinical studies subjects with a history of major renal abnormalities were excluded. In subjects with mild to moderate renal impairment (creatinine clearance =30-80 ml/min), the mean AUC and C_{max} of the N-desmethyl metabolite increased about 126% and 73% respectively compared to healthy subjects. However, due to high inter-subject variability, these differences were not statistically significant. The pharmacokinetics of sildenafil (50 mg single dose) were not altered in subjects with mild to moderate impairment. The dosing recommendation has been addressed in the SPC.

After a single dose of 50 mg sildenafil in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B), the systemic exposure (AUC) of sildenafil increased significantly, by about 80%. A decrease in blood pressure was detected. The pharmacokinetics and safety of sildenafil have not been investigated in patients with severe hepatic dysfunction: this population is therefore contraindicated.

Healthy elderly subjects (65-81 years) showed a statistically significant increase in AUC of sildenafil and the N-desmethyl metabolite of about 90% compared to young healthy subjects (18-45 years). The increase in free sildenafil plasma concentration was approximately 40%. A first dose of sildenafil 25 mg should be used in the elderly. However, the Phase II/III trials showed that the incidence of adverse events did not increase with age.

Sildenafil is not indicated for children under 18 years. Sildenafil is not indicated for use by women.

Population pharmacokinetic analysis carried out on five Phase III studies showed similar results to those observed in individual pharmacokinetic studies, e.g. alteration of sildenafil absorption rate with food, reduced sildenafil clearance with hepatic status, with increasing age and with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). No effect was found on sildenafil pharmacokinetics with concomitant administration of CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP 450 metabolism (such as rifampicin, barbiturates). In addition, no correlation was found between alcohol intake or smoking status and sildenafil pharmacokinetics.

Efficacy

Four main therapeutic efficacy studies* of double-blind, placebo-controlled, parallel-group, fixed dose (148-102, 148-364) and flexible dose design (148-103, 148-363) were performed to investigate the efficacy of sildenafil in the claimed indication (see Table 1 below). In addition, among other supportive studies, two** were conducted in spinal cord injury (148-367, crossover design) and diabetic patients (148-104, parallel group), also titrating doses. Overall, efficacy data (main and supportive studies) were evaluated from more than 3000 patients receiving sildenafil (aged 19-87). No comparison with locally injected vasodilators was investigated, as this mode of administration precluded relevant blinded comparison.

| Study 148- | Design | Aetiology | Sildenafil (mg) | Subject number | Duration |
|------------|---------------------------------------|--------------------|---------------------|----------------------|--------------------|
| 102* | Phase III, DB, PC, parallel, fixed | Broad-spectrum | 25, 50, 100 placebo | 102, 107, 107 216 | 24 weeks |
| 364* | Phase III, DB, PC, parallel, fixed | Broad-spectrum | 25, 50, 100 placebo | 128, 132, 127 127 | 12 weeks |
| 103* | Phase III, DB, PC, parallel, flexible | Broad-spectrum | 25-100++ placebo | 163 166 | 12 weeks |
| 363* | Phase III, DB, PC, parallel, flexible | Broad-spectrum | 25-100++ placebo | 159 156 | 26 weeks |
| 104** | DB, PC, parallel, flexible | Diabetes | 25-100++ placebo | 136 132 | 12 weeks |
| 367** | DB, PC, 2-crossover, flexible | Spinal cord injury | 25-100++ placebo | 175 174 | 6 weeks/ period |

DB: double-blind; PC: placebo controlled.

Patient population – Male subjects with a primary clinical diagnosis of erectile dysfunction of more than 6 months duration were included (psychogenic, organic or mixed aetiology). The following patient groups were represented: elderly (21%), patients with hypertension (24%), diabetes mellitus (16%), ischaemic heart disease and other cardiovascular diseases (14%), hyperlipidaemia (14%), spinal cord injury (6%), depression (5%), transurethral resection of the prostate (5%), radical prostatectomy (4%). The following groups were not well represented or excluded from clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (i.e. a history of stroke or myocardial infarction within the previous six months or cardiac failure, unstable angina or life-threatening arrhythmias within the previous six months). Other excluded patient populations included those on certain concomitant therapies (i.e. trazodone, testosterone or any other therapies to treat ED) and patients with known raised prolactin or low free testosterone levels, hypotension (i.e. a resting sitting BP <90/50 mmHg), retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases), untreated diabetic proliferative retinopathy, active peptic ulcer disease, and unstable medical conditions. More than 90% subjects were Caucasian.

Efficacy parameters – It has been assumed that sexual function is best assessed in a natural (home) setting with patient self-reporting by means of questionnaires, which is preferable to a laboratory setting with objective measures such as the RigiScan device. The International Index of Erectile Function (IIEF) was developed as a brief, reliable and validated measure of male sexual function, which contains 15 questions allocated to one of five domains of sexual function (erectile function, orgasmic function, sexual desire, intercourse and overall satisfaction); each question could be answered on a 5 or 6-point scale. The primary efficacy endpoints were responses to Questions 3 and 4 of this IIEF questionnaire, which assessed ‘how often the subject was able to penetrate his partner’ and ‘how often the subject was able to maintain the erection after penetration’. The secondary efficacy endpoints were based on responses to the remaining IIEF questions, the partner questionnaire, the overall efficacy assessment, the event log of erectile function, quality of life questionnaire, and discontinuation due to lack of efficacy and others. Efficacy evaluation was based on the intent to treat (ITT) population.

Primary analysis

Main studies – The efficacy of sildenafil 25, 50 and 100 mg was compared to placebo in the two fixed dose studies (studies 102, 364), while in the two placebo flexible dose studies, subjects started on a dose of 50 mg (study 103) or 25 mg (study 363) and were allowed to adjust the dose up or down based on efficacy and toleration. Subjects take the dosage as required approximately one hour prior to sexual activity.

The ITT analysis (fixed dose studies) indicated superiority of sildenafil over placebo at all doses in terms of the main endpoints (Table 2). Sildenafil groups showed mean values at 3 months of about ‘3’ with 25 mg (‘sometimes, about half the time’), between ‘3’ and ‘4’ with 50 mg, and almost ‘4’ with

100 mg ('most times, much more than half the time') for questions 3 and 4. The response at 6 months was similar to the response observed at 3 months (study 102).

In both flexible dose studies, the ITT analyses at week 12 demonstrated a statistically significant treatment effect of sildenafil. A greater proportion of sildenafil treated subjects with initial low baseline responses (51% and 55% in studies 363 and 103, respectively) were able to regularly achieve and maintain erections when compared with placebo (9% and 6% in studies 363 and 103, respectively).

Analysis in all four studies of scores obtained on both IIEF questions resulted in a statistically significant treatment effect, with a dose-related increase in the mean response scores in subjects taking sildenafil (Table 2).

Similar results in direction and magnitude were also observed in supportive studies conducted in subjects with ED of broad spectrum aetiology.

Table 2 - Mean scores for subjects in main studies responding to questions 3 and 4 at week 12:

| ITT week 12 | Q.3: 'how often the subject was able to penetrate his partner' | | | | Q. 4: 'how often the subject was able to maintain the erection after penetration' | | | |
|------------------------------|--|-----------------------|---------|---------------------------|---|-----------------------|---------|---------------------------|
| | N | Overall baseline mean | LS mean | Overall treatment p-value | N | Overall baseline mean | LS mean | Overall Treatment p-value |
| Flexible dose studies | | | | | | | | |
| Study 103 | | 2.03 | | <0.0001 | | 1.52 | | <0.0001 |
| placebo | 138 | | 2.28 | | 138 | | 1.79 | |
| Sildenafil+ (25-100 mg) | 138 | | 3.87 | | 137 | | 3.63 | |
| Study 363 | | 1.89 | | <0.0001 | | 1.63 | | <0.0001 |
| placebo | 118 | | 2.16 | | 116 | | 2.07 | |
| Sildenafil+ (25-100 mg) | 136 | | 3.54 | | 136 | | 3.53 | |
| Fixed dose studies | | | | | | | | |
| Study 102 | | 1.98 | | <0.0001 | | 1.58 | | <0.0001 |
| placebo | 190 | | 2.31 | | 189 | | 2.20 | |
| 25 mg | 95 | | 3.27+ | | 95 | | 3.15+ | |
| 50 mg | 100 | | 3.65+ | | 100 | | 3.51+ | |
| 100 mg | 96 | | 3.99+ | | 96 | | 3.94+ | |
| Study 364 | | 2.20 | | <0.0001 | | 1.83 | | <0.0001 |
| placebo | 117 | | 2.17 | | 115 | | 1.96 | |
| 25 mg | 121 | | 3.18+ | | 119 | | 2.99+ | |
| 50 mg | 123 | | 3.65+ | | 122 | | 3.40+ | |
| 100 mg | 120 | | 3.79+ | | 118 | | 3.63+ | |

Statistical test used: ANCOVA; LS = Least Squares (adjusted) mean

Scores 0-5 with 1 = almost never/never and 5 = almost always/ always, 0 = did not attempt sexual intercourse

* Indicates last observation up to 99 days; + Sildenafil versus placebo for Questions 3 and 4, p<0.0001.

Secondary analysis - In all four of the main studies, a statistically significant treatment effect ($p < 0.0001$) was shown for sildenafil treated subjects in 4 domains of the IIEF questionnaire (erectile and orgasmic function, intercourse and overall satisfaction).

The *Global Assessment Question* (GAQ) was asked after 12 weeks treatment. Overall, a statistically significant number of subjects reported an improvement in their erections after receiving sildenafil compared to those receiving placebo.

An *Event Log* (a record of successful attempts at sexual intercourse) was to be completed each time study medication was taken or the subjects engaged in sexual activity. At the recommended doses (excluding study 104 in diabetics), 62-73% of the attempts at intercourse were successful in the various sildenafil groups compared to 22-25% of attempts in the placebo group. A dose response relationship was not obvious. Overall there was no benefit of 200 mg over 100 mg of sildenafil.

A *Partner Questionnaire* asking similar questions to the primary endpoints indicated homogeneous results in magnitude and direction in favor of subjects treated with sildenafil.

Quality of Life assessment showed positive effects for sildenafil regarding the relationship with partner, emotional control, general health, the impact of emotional problems on daily functioning, and aspects of emotional distress associated with having an erectile problem.

In the main fixed dose studies, more subjects allocated to placebo treatment experienced a lack of efficacy compared to the sildenafil treated group. *Discontinuation* rate due to lack of efficacy was 5.0% for subjects receiving placebo vs. 2.6% for sildenafil treated subjects on 25 mg, 0.8% for subjects on 50 mg and 0% for subjects on 100 mg.

Dose response - Overall, a dose-related increase in mean response scores was observed in the fixed dose studies (studies 101/101B, 102, 106, 361 and 364), between 25 mg and 100 mg sildenafil, reaching a plateau at 100 mg. Similar response scores were shown between subjects taking the 100 mg and 200 mg doses. In the main flexible dose studies, 23% (starting dose of 50 mg) and 28% (starting dose of 25 mg) remained at their first level of dose. When the starting dose was 50 mg (study 103), at the end of the trial 74% of patients were taking 100 mg and only 2% of patients had decreased their dose from 50 mg to 25 mg due to adverse events. Where the starting dose was 25 mg (study 363), 44% of patients were taking 100 mg and 28% were taking 50 mg at the end of the trial.

Long-term efficacy - Double-blind long-term efficacy evaluated up to 24 weeks (studies 102, 101/101B, 356) and 26 weeks (study 363) indicated that the responses reached at an early stage were maintained until the end of the follow-up. At the end of the initial open treatment period in study 356 (16 weeks treatment), 96% of subjects (207 of 216) wanted to continue treatment and 93% (200 of 216) felt an improvement in their erections. The majority of subjects randomised in the 8-week follow-up phase to double-blind placebo, reported that their erections were worse than those when they received open sildenafil. Long-term efficacy based on a median therapy duration of 358 days (study 354A) showed that, of the subjects responding, 22%, 47%, 15% and 16% had a final dose of 25 mg, 50 mg, 75 mg and 100 mg, respectively. Overall 91% of subjects in open label studies wanted to continue treatment.

Factors influencing response - Analysis of covariance in the main studies has been used to evaluate the effect of other possible explanatory variables on the primary endpoint measurements.

There was no clear-cut consistent *age* effect, but a trend toward slightly lower scores on the IIEF questions 3 and 4 occurred with subjects > 65 years of age. *Duration of ED at baseline* and other *clinically relevant variables* (such as depression, cardiovascular disease, and hypertension) did not have any apparent effect on therapeutic response. However, the *severity of ED at baseline* was found to have a statistically significant effect on response to IIEF questions 3 and 4.

In the main studies, *etiology* did not show evidence of interaction in any primary endpoint analyses, but did have a statistically significant effect on the global assessment of improvement in erections. The highest response for improvement in erections was observed in subjects with psychogenic ED, followed by mixed etiology and organic ED. Patients with radical prostatectomy showed a lower (but still effective) response (IIEF Questions 3 and 4) to sildenafil than non-prostatectomy patients.

There was no evidence of any interaction with treatment based on a subgroup analysis with 343 *diabetic subjects* treated with sildenafil and 232 treated with placebo. Although response scores were

generally lower in diabetic subjects compared to the broad-spectrum population (mean score of 2.90 and 2.71 for questions 3 and 4 in diabetic subjects, respectively, versus a mean score of 3.58 and 3.46 in non-diabetic subjects), sildenafil was shown to be effective. These data are consistent with the results of a specific study evaluating the effect of sildenafil during 12 weeks in diabetic patients (study 104).

Sildenafil was superior to placebo in primary and secondary endpoints (study 367) in subjects with *spinal cord injury* of various severities, including subjects with complete transection of the spinal cord.

Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), trans-urethral resection of prostate (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%).

Safety

The assessment of the safety of sildenafil is based on pooled data from 4213 subjects enrolled in double-blind, placebo controlled Phase II/III clinical studies, including 3003 sildenafil treated subjects and 1832 placebo treated patients. In addition, 769 subjects on placebo in placebo-controlled studies received sildenafil in open-label extension studies. Among the sildenafil treated group, 1682 subjects received a starting dose of 50 mg or greater and 559 subjects had a duration of sildenafil therapy of at least one year. In general, 8-9 doses per month were taken during the first months and, from the fifth month onward, the frequency of dosage decreased to an average of 3 doses per month.

As of February 1997, 13 deaths have occurred in the sildenafil group and 2 in the placebo group. None of them were considered to be related to treatment, and the death rate (per 100 man years of treatment) was comparable for sildenafil and placebo groups. In the overall safety database, no differences were observed in the rate of all cardiovascular serious adverse events and the rate of myocardial infarctions adjusted to 100 man years of treatment. An additional overview of deaths from the clinical trial's database as of 1 May 1998 was provided, reporting overall 22 deaths on sildenafil treated group (several days after last dose) and 2 deaths on placebo. Similar death rates per 100 man years were observed (0.45 on sildenafil, 0.57 on placebo). None of the death were considered to be related to sildenafil. Post marketing, the Marketing Authorisation Holder has provided updated information on the incidence of myocardial infarction and of all cause mortality from their safety database, including data from ongoing or completed clinical trials. On the basis of the data provided, the overall safety of sildenafil was considered acceptable.

In the placebo controlled phase II/III studies, the overall frequency of *discontinuation* was 8.5% for sildenafil treated subjects and 13.9% for placebo treated subjects (Table 3). Premature discontinuation due to adverse events related to study drug was higher in the sildenafil treated population (1.4% vs. 0.7%), but pooling data of adverse events (related and not related to study drug) demonstrated comparable results (2.6% vs. 2.3%).

The rate of discontinuation from the study due to cardiovascular adverse events in placebo-controlled studies was low for both sildenafil (all causality: 0.9%, treatment-related: 0.3%) and placebo (all causality: 0.9%, treatment-related: 0.2%) groups. The rate of discontinuation from the study due to body as a whole adverse events was 1.7% for sildenafil and 0.8% for placebo. Most cases of abnormal vision reported did not lead to discontinuation. Discontinuation due to gastrointestinal adverse events was more frequently observed in sildenafil group (0.8%) compared to placebo group (0.4%). Discontinuation due to laboratory abnormalities did not increase with increasing dose of sildenafil.

Table 3: Summary of discontinuation from study in Phase II/III placebo-controlled Studies.

| | Number (%) of Subjects | |
|-----------------------------|------------------------|------------|
| | Sildenafil | Placebo |
| Total treated | 2722 | 1552 |
| Discontinued | 230 (8.5) | 215 (13.9) |
| Related to study drug | 83 (3.1) | 101 (6.5) |
| Adverse event | 37 (1.4) | 11 (0.7) |
| Laboratory abnormality | 4 (0.2) | 5 (0.3) |
| Lack of efficacy | 42 (1.5) | 85 (5.5) |
| Not related to study drug * | 147 (5.4) | 114 (7.4) |
| Adverse event | 32 (1.2) | 25 (1.6) |
| Laboratory abnormality | 8 (0.3) | 6 (0.4) |
| Special Safety test | 1 (0.0) | 0 |
| Subject died | 3 (0.1) | 0 |

*Reasons for discontinuation not related to study drug also include: does not meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, and others.

An analysis of the overall number of *adverse events* as well as treatment related adverse reactions on the recommended doses (25-100 mg) resulting from placebo controlled studies (n=2722 for sildenafil, n=1552 for placebo), showed a higher overall incidence rate in subjects treated with sildenafil compared with placebo. The overall incidence for all causality adverse events in placebo controlled studies was 64.9% for sildenafil and 42.7% for placebo. Treatment-related adverse events occurred in 37.2% of sildenafil treated patients and 9.6% placebo treated patients. Headache, vasodilation (flushing), dyspepsia, rhinitis and abnormal vision were the most frequently encountered side effects.

The overall incidence of treatment-related *cardiovascular adverse events* was higher in sildenafil treated subjects (17%; 464/2722) than in subjects receiving placebo (4.8%; 75/1552), the majority of which were due to vasodilatation. Headache and vasodilatation (flushing) were responsible for the majority of all adverse events reported in sildenafil-treated subjects, and the majority of these complaints were mild or moderate in severity. All causality incidences of adverse events associated with changes in blood pressure were comparable for sildenafil and placebo (syncope 0.1% vs. 0.3%, hypotension 0.3% vs. 0.1%, dizziness 2.7% vs. 1.4% and postural hypotension 0.1% vs. 0.1%). There were no differences in incidence of myocardial infarction or other serious adverse events between groups. Patients with recent (<6 months) myocardial infarction, unstable angina, cardiac failure or life threatening arrhythmia were excluded from clinical trials.

As was the case in the initial clinical trials, serious cardiac and vascular events including myocardial infarction, angina pectoris intermediate syndrome, sudden cardiac deaths, ventricular arrhythmias, cerebrovascular haemorrhage, transient ischemic attack, hypertension and hypotension, occurring in temporal association with the use of Viagra have been reported post marketing. Most but not all occurred in patients with pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse, and a few were reported to occur shortly after the use of Viagra without sexual activity. Although in some cases there was a temporal association with the use of Viagra and sexual intercourse, it is not possible to determine whether the events were due to underlying disease or risk factors, sexual intercourse, Viagra, or to other unknown factors.

The overall incidence of abnormal vision (in all placebo-controlled studies) was 6.5% versus 0.4% for sildenafil and placebo respectively. Abnormal vision was commonly described as a transient color tinge to vision, an increased perception of light or blurred vision. Most cases of abnormal vision were considered as mild or moderate in severity, and did not lead to discontinuation. Patients with untreated proliferative diabetic retinopathy or macular degeneration have not been included in the clinical studies in significant numbers. However, diabetic patients in placebo-controlled studies did not show a higher frequency of abnormal vision than non-diabetic patients (6.0% versus 6.6%, respectively).

Further studies as part of post-marketing surveillance program have been requested to investigate the consequences of long-term therapy.

The overall incidence of gastrointestinal adverse events in all placebo controlled studies was 19.3% for sildenafil and 7.3% for placebo. The overall incidence increased with dose and the incidence decreased as duration of treatment increased. Dyspepsia of mild or moderate severity was the main gastrointestinal adverse event reported and is probably related to the pharmacological action of sildenafil.

Pooled safety data indicated that myalgia occurred more frequently in subjects treated with sildenafil than placebo (2.1% vs. 0.8%). Additional laboratory tests did not show any significant findings. Several cases reported the pain to be severe (5 out of 49 in sildenafil group and 2 out of 12 in placebo group). The incidence of myalgia increased as the dose of sildenafil was increased from 50 to 100 mg, but did not increase further when the dose was increased to 200 mg.

No significant differences in the overall incidence of adverse events for subjects treated with sildenafil with or without concomitant therapies (anti-anginal, antihypertensive, antidepressant and CYP 2C9 inhibiting agents) were observed. Nevertheless, in sildenafil subjects treated with CYP 3A4 inhibiting medication, the overall incidence of adverse events was higher than in subjects without co-administration (76.0% vs. 62.7%, respectively) and this has been addressed in the SPC. No apparent age related differences in the incidence of adverse events and the rate of discontinuations from the studies were observed.

Incidence of clinically significant *laboratory* changes and median changes in laboratory parameters, median changes of vital signs, and ECG changes have been assessed, and were in general similar for subjects receiving sildenafil and in those receiving placebo. However, a higher incidence of hemoglobinuria (16.7% for sildenafil vs. 6.8% for placebo), the majority of which were judged to be spurious laboratory data, and creatine kinase (2.3% vs. 1.2% respectively) were seen.

There were no reports of priapism in clinical trials. In postmarketing surveillance, priapism has been reported.

5. Conclusion and risk/benefit assessment

Quality

The quality of sildenafil film-coated tablets, as demonstrated in the chemical, pharmaceutical documentation, is acceptable.

Preclinical pharmacology and toxicology

The preclinical pharmacodynamic studies have shown that sildenafil has a high potency and selectivity for PDE5 relative to other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. Sildenafil can potentiate the rise in intracavernosal pressure induced by stimulation via smooth muscle relaxation. Pharmaco- and toxicokinetics were also adequately studied. The main toxicity findings are well characterised and do not raise concern for human safety.

Efficacy

Based on the pharmacodynamic, safety and tolerability results, it was decided to study doses of 25, 50 and 100 mg in the clinical studies. The clinical efficacy of sildenafil was well established with regard to attaining and maintaining erections sufficient for sexual intercourse in male subjects in a broad spectrum of etiology over a 3 months follow-up period, including diabetes and spinal cord injury. In order for sildenafil to be effective, sexual stimulation is required. In dose ranging from 25-100 mg a statistically significant improved response with sildenafil was observed compared to placebo treatment. A dose related increase in response was observed up to 100 mg. However, there was no improvement in efficacy with increasing dose to 200 mg but the incidence of adverse reactions was increased. In general, the clinical trials support the starting dose of 50 mg sildenafil with the option to increase to 100 mg or decrease to 25 mg. All secondary endpoints corroborated the findings of the primary endpoints. Substantially more subjects in the main fixed dose studies allocated to placebo

treatment discontinued due to lack of efficacy, and the discontinuation rate (due to lack of efficacy) in the sildenafil group decreased as the dose of sildenafil increased.

Safety

An analysis of the overall number of adverse events as well as treatment related adverse reactions on the recommended doses (25-100 mg) showed a higher overall incidence rate in subjects treated with sildenafil compared with placebo. Headache, flushing, dyspepsia, nasal congestion and altered vision are the most frequently encountered side effects. The majority of the reported adverse events were mild to moderate in severity. Premature discontinuation due to study drug related adverse events was comparable for the sildenafil and placebo group. The incidence of adverse events increased with increasing dose and decreased as duration of treatment increased. No differences were observed in the overall safety database for mortality, all serious cardiovascular adverse events, and myocardial infarction (rate adjusted to 100 man years of treatment). On the basis of the data provided, the overall safety profile of sildenafil is considered acceptable. The safety concerns with the use of sildenafil have been addressed in the SPC with the inclusion of appropriate warnings, precautions, and contraindications. In addition, the company accepted to update the safety database frequently so as to incorporate relevant information on the use of the drug in clinical practice on an ongoing basis as the medicinal product is released in different countries, and also to perform prescription event monitoring (PEM) studies once it is released in the EU. Updated information from the Marketing Authorisation Holder including data from ongoing and completed clinical trials has been submitted. As was the case in the initial clinical trials, some serious cardiovascular events were reported post marketing, occurring mostly in patients with pre-existing cardiovascular risk factors. Although in some cases there was a temporal association with the use of Viagra and sexual intercourse, it is not possible to determine whether the events were due to underlying disease or risk factors, sexual intercourse, Viagra, or to other unknown factors.

Risk/benefit assessment

The relative benefit/risk ratio of sildenafil in the treatment of ED is favourable. No comparative studies with locally active agents were performed for ethical and methodological reasons. The clinical efficacy of sildenafil was well established with regard to attaining and maintaining erection sufficient for satisfactory sexual performance in male subjects in a broad spectrum of etiology over a 3 months follow-up period, including patients with diabetes and spinal cord injury. In dose ranges from 25-100 mg, a significantly improved response with sildenafil was observed compared to placebo treatment.

Since sildenafil was shown to potentiate the hypotensive effects of nitrates, its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contra-indicated. Several special patient groups, those excluded from the clinical studies (severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as *retinitis pigmentosa*) and those for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure) have been contra-indicated.

The proposed starting dose of 25 mg sildenafil should be considered for those with severe renal impairment, hepatic impairment and those taking concomitant CYP3A4 inhibitors including HIV protease inhibitors, since sildenafil clearance is reduced in these populations. Coadministration of sildenafil and ritonavir is not advised, but if considered necessary, a maximum sildenafil dose of 25 mg once every 48 hours should not be exceeded.

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered.

Questions were raised with regard to the visual disturbances caused by sildenafil. The SPC includes an appropriate contraindication in the appropriate subgroups to ensure visual safety.

The legal status was considered and it was agreed not to restrict the prescription status. Clarification was requested from the company on the usage/marketing surveillance of sildenafil (e.g. educational training materials for the prescriber).

Taking into consideration the data provided, the overall safety issues and the benefit to risk balance, as well as the commitments to be undertaken by the company, the CPMP considered the benefit to risk assessment positive and recommended the granting of a Marketing Authorisation for all strengths and presentations of this medicinal product. The product is authorised for the indication ‘treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance’.

Upon the 5-year renewal assessment (July 2003), the CHMP concluded that the safety and the efficacy of this medicinal product continued to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of VIAGRA continues to be favourable for the treatment of men with erectile dysfunction.