SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cialis. For information on changes after approval please refer to module 8.

Introduction

Male erectile dysfunction has been defined as the persistent inability to attain and maintain an erection adequate to permit satisfactory sexual performance.

Although erectile dysfunction is regarded as a benign disorder, it has a medical and social impact due to its high prevalence, costs and implications for the quality of life for many men and their partners. A recent review concludes that the prevalence of erectile dysfunction of all degrees is 52% in men 40 to 70 years old, with the incidence increasing with advancing age.

Normal erectile function requires the coordination of psychological, hormonal, neurological, vascular and anatomic factors. Alteration of any of these factors is sufficient to cause erectile dysfunction. Main causes of erectile dysfunction are chronic systemic illnesses such as diabetes mellitus, heart disease, hypertension and peripheral vascular disease. Neurological disorders, such as post-traumatic spinal-cord injuries, multiple sclerosis or post-surgical lesions such as radical prostatectomy are also important causes of erectile dysfunction. Hormonal disorders such as hyperprolactinemia, local conditions as Peyronie's disease or congenital or trauma deformities of the penis, drug-induced erectile dysfunction (antidepressants, thiazides, anabolic steroids, cimetidine, digoxin, or metoclopramide) and psychogenic factors are other frequent causes of erectile dysfunction.

There are several approaches to the management of erectile dysfunction: psychosexual counselling, hormonal therapy, mechanical devices, vascular surgery and pharmacological treatment.

Psychosexual counselling can be useful in patients who have a considerable psychogenic component and it is usually used in conjunction with drug treatment.

The hormonal therapy may benefit patients who are diagnosed with hypogonadism. Mechanical devices such as vacuum constriction devices are a non-invasive method, but their main disadvantages include discomfort, borderline erection quality and psychological objections to the mechanical aspect of the treatment. Penile prostheses are recommended when other treatments have failed.

Vascular reconstructive surgery is sometimes indicated in patients suffering from arterial or venous occlusive disease, often as the last resort before the implantation of a penile prosthesis.

With regards to the pharmacological treatment therve are three alternatives: oral treatment, penile injection therapy and intraurethral therapy.

Since the introduction of sildenafil (Viagra ™) in 1998, as the first widely used oral treatment for erectile dysfunction, the pharmacological treatment has acquired a more relevant role in the management of the disease.

Tadalafil (CIALIS®) is an orally administered phosphodiesterase type 5 (PDE5) inhibitor that has been developed as a treatment for erectile dysfunction. When sexual stimulation causes the local release of nitric oxide, which plays a central role in the vasodilation of erectile tissues by stimulating guanylyl cyclase activity, consequently raising intracellular concentrations of cyclic guanosine monophosphate (cGMP) and relaxing vascular smooth muscle. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection.

Thus tadalfil is indicated for the treatment of erectile dysfunction. Tadalafil has no effect in the absence of sexual stimulation.

Chemical, pharmaceutical and biological aspects

Composition

Cialis contains 10 mg or 20 mg of tadalafil as active ingredient presented in the form of film-coated tablets.

Conventional pharmaceutical excipients are used: lactose monohydrate, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, microcrystalline cellulose and magnesium stearate (vegetable source), and Opadry II Yellow.

Cialis tablets are packaged in 2 mil Aclar blisters with PVC with an aluminium foil lid.

Active substance

Tadalafil INN is Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione,6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-,(6R-trans)-(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl]-pyrazino[1',2':1,6] pyrido [3,4-b]indole-1,4-dione.

Tadalafil is practically insoluble in water. It does not possess any ionisable groups in the pH range of 1-11 and, subsequently, does not demonstrate any changes in solubility in aqueous buffers in that range. It is freely soluble only in solvents such as dimethylsulfoxide and dimethylformamide.

This molecule has 2 chiral centres, and therefore four different stereoisomers may be found. The molecule obtained in the process described is in the RR form.. Crystallization studies show that tadalafil does not exhibit polymorphism.

Tadalafil drug substance is synthesised by a 3-step process, with purifications following each step. After the final drying, the resulting solid is milled to meet the established particle size specification."

Active substance specification

The active substance specification includes tests for identity (IR, HPLC), assay and a number of purity tests for related substances (HPLC), residual solvents (GC), and other appropriate tests.

The analytical methods used in routine controls are suitability described. The validation studies submitted are in accordance to the ICH Guidelines on "Validation of Analytical Procedures". Impurity limits in the specification are justified by toxicology studies.

Batch data are provided for 14 production batches and 14 batches manufactured using a previous manufacturing process, as supporting data..

The tests and limits in the specification are appropriate for controlling the quality of Tadalafil.

Stability

Stability studies under stress conditions and formal stability studies were carried out in five batches of drug substance manufactured by the commercial process. Three of them were packaged in container closures identical to those intended for use in commercial distribution with and without desiccant. The other two batches were stored in double 4-mil LLDPE liners in a foil laminate liner in fibre drums without desiccant.

Analytical methods used for stability studies are the same or equivalent to those used for release testing of the active substance. Other tests were also investigated as part of the comprehensive stability package.

Stability Studies on the solid state, solutions and suspensions of the active substance at different conditions were carried out. No degradation or physical changes were observed in tadalafil at its solid state under heat, humidity and light exposure. However, degradation was observed in solutions and suspensions of the active substance at different pH values, light and oxidative conditions.

Tests were carried out following the ICH stability guideline
All tests are carried out in these studies are sufficient to establish the retest period for tadalafil, two years.

Other Ingredients

Conventional pharmaceutical excipients lactose monohydrate, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate (vegetable origin), hypromellose, triacetin, titanium dioxide (E171), iron oxide (E172), and talc are of Ph. Eur/ USP/JP quality. Certificates of analyses are provided and show compliance with respective monographs. The Magnesium stearate is of vegetable origin, and a statement concerning the absence of risk for TSE transmission is provided.

The composition of the excipients not described in a pharmacopoeia (colour mixture yellow 32K12884) is enclosed in the dossier, joined to the specification for identification and microbial limits.

Description of the packaging material and IR spectra of each component is included. Quality specifications and routine tests for all these materials are described.

Product development and finished product

The development pharmaceutics have taken into consideration the physicochemical characteristics of the active drug substance such as poor aqueous solubility, hygroscopic properties, stability, particle size, and biopharmaceutical issues such as dissolution rate.

The formulation contains stable, milled tadalafil drug substance and incorporated into a wet granulation to consistently produce tablets with good homogeneity and the desired dissolution characteristics. To achieve a dosage form with a rapid therapeutic onset, the excipients included in the formulation were selected and adjusted to promote rapid absorption. This combination of ingredients has produced a material (free-flowing, easily wetted and compressible) as well as tablets that possess the desired physical characteristics of low friability, acceptable hardness and rapid disintegration. After that, film coating stage produce film-coated tablets with a uniform appearance, easy to swallow with little or no impact on the dissolution profile

Clinical trial studies were performed using different formulations and they have shown to be bioequivalent with the market formulation.

The process for the manufacturing of the finished product follows conventional pharmaceutical practices, which includes aqueous wet granulation, sizing, and drying steps of tadalafil with hydrophilic excipients, followed by dry sizing of the granulate and then blending with additional excipients. The final blend is compressed into tablets, which are subsequently coated.

Validation of the manufacturing process was performed on 3 full-scale batches. For each one of those batches, specific conditions at each stage were investigated (mixing speeds, times, screen size, temperature, rotation speeds, etc.). Results indicate that the process is adequately validated and controlled.

Product Specification

The specification includes tests by validated methods for appearance, water content, microbial purity (Ph Eur), dye identity test, dissolution (UV, HPLC), identification (IR), assay (HPLC), content uniformity (UV), and degradation products (HPLC).

The *dissolution test* is performed in a dissolution apparatus. Either UV spectrometric or HPLC detection quantified the drug dissolved. The dissolution procedure is validated with respect to precision and robustness. The two detection methods are validated in terms of accuracy, precision (repeatability and reproducibility), specificity, linearity, range and robustness.

There are no solid-state degradation products and chemical stability has been maintained under all experimental storage conditions. However, limits for individual related substances and total related substances are established at release and shelf life, even when these products have not been observed. Limits for individual and total related substances are established based on active substance limits and the “CPMP/ICH guideline on impurities in new products”.

The tests and limits of the release and shelf life specification for the finished product are appropriate to control the quality of CIALIS for their intended purpose.

Batch data are provided for 14 production scale batches and indicate satisfactory uniformity.

Stability of the Product

Results are generated under ICH conditions for batches of tablets stored up to 12 months.

The characteristics studied are appearance, water content, dissolution, degradation products and assay. Analytical methods used for primary stability studies are the same as those used for release testing of the drug product. These methods are adequately validated.

The quality specifications at shelf life were provided.

The primary and supporting stability batches of tadalafil film-coated tablets demonstrate that the drug product is stable at room temperature.

As a conclusion from the stability studies, the results indicate satisfactory stability and support the shelf life stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Cialis is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. The excipients are commonly used in this kind of formulation; the packaging material is well documented and meets Ph Eur requirements. The manufacturing process of finished product has been adequately described. The quality defined is supported by all data provided in the dossier.

The stability of the finished product in the proposed packaging has been adequately demonstrated and supports the proposed expiry data.

Toxico-pharmacological aspects

Pharmacodynamics

CIALIS contains the active substance tadalafil, a new reversible inhibitor of the cyclic guanosine monophosphate (cGMP) phosphodiesterase, PDE type 5 (PDE5), intended for the treatment of male erectile dysfunction.

- *In vivo* studies

Although no *in vivo* study has been carried out, results of *in vitro* studies conducted indicate that tadalafil exerts PDE5 inhibitor activity suggesting that it can be efficacious in the treatment of patients with erectile dysfunction.

- General and safety pharmacology programme

In anaesthetised dogs, a 3-mg/kg intravenous dose reduced blood pressure due to the vasodilator activity without affecting cardiac output, and in conscious dogs oral doses up to 200 mg/kg had no effect on heart or respiration rate or ECG waveform. There were no changes in PR and QT intervals produced by tadalafil or, by inference, its metabolites.

Additional data from clinical studies was provided on the effects of tadalafil on platelet and retinal function. There were no treatment-related effects observed on bleeding time and also, no effects of tadalafil on retinal function were observed. The effect of tadalafil on *in vitro* cardiac electrophysiology has not been investigated. However no tadalafil-related adverse cardiovascular effects were observed. Since its potential effects on cardiac electrophysiology are based on clinical data, the Applicant has committed to conduct a HERG channel assay with tadalafil as a post-authorisation follow-up measure.

Pharmacokinetics

A number of studies have been carried out to characterise the pharmacokinetic profile of tadalafil. Tadalafil was absorbed in mice, rats, and dogs, but the extent of absorption varied with dose. In general, plasma levels of tadalafil increased with dose in mice, rats, and dogs, but the increases were less than proportional, especially at the higher doses used in the toxicology studies. A prolonged absorption phase was observed in all species at these high doses.

Following absorption, tadalafil was extensively bound to plasma proteins in mice, rats, and dogs. Tadalafil was shown to be widely distributed in animal tissues, the highest levels being observed in the gastrointestinal tract contents and the liver. Tadalafil was not observed in the central nervous system. No studies have been reported using multiple dose regimens. The lack of such studies is justified taking into account the proposed dose regimen.

All the metabolites found in humans have been identified in animal species. The major routes of metabolism followed an initial opening of the methylenedeoxybenzyl ring to form the catechol. The catechol undergoes glucuronidation to form the catechol glucuronide conjugate or extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively.

The major route of excretion of tadalafil was via the faeces both in rats and dogs, indicating incomplete oral absorption and biliary excretion of metabolites. Very little urinary excretion occurred in rats and it was a minor route of elimination in dogs.

In assessing the exposure margins in the animals used during toxicology studies, with those in humans, systemic exposure to tadalafil was observed during the toxicity studies providing margins of safety above those that are achieved in humans after a 20 mg dose.

In vitro studies with human liver microsomes and cultured human hepatocytes showed that tadalafil caused both mechanism-based inhibition of CYP3A4 activity (at micromolar concentrations) and induction of CYP3A4 expression. Additional data on possible drug-drug interactions between tadalafil and other concomitantly administered drugs that are metabolised via CYP3A4 were submitted during the procedure. These were clinical data in relation to interaction studies conducted with tadalafil and concomitantly administered midazolam or lovastatin to determine *in vivo* whether tadalafil could affect metabolism of drugs metabolised by CYP3A4. The pharmacokinetics of midazolam and lovastatin in healthy subjects were virtually unaffected by co-administration with 10 and 20 mg respectively of tadalafil, indicating that tadalafil is unlikely to interfere with CYP3A4 metabolism of other interaction drugs. This information has been included in the Summary of Product Characteristics (SPC), specifically stating that most of interaction studies were performed at dosage of 10 mg.

Toxicology

A battery of toxicity studies was conducted in order to assess the possible toxic effects that could be due to tadalafil. There is no concern in relation to GLP fulfilment.

- Single dose toxicity:

In single-dose toxicity studies, tadalafil by the oral route was well tolerated in mice and rats and by intravenous route tadalafil at 62.5 mg/kg resulted in clinical signs including tremors and laboured breathing in mice, and moribund condition and convulsions in some rats. For both species, the clinical signs were limited to the day of dosing, and the control groups displayed some of the same clinical signs as treated animals at the higher doses. It has been suggested that it may be related to the 90% PEG 400 vehicle.

- Repeat dose toxicity:

In chronic toxicity studies main toxic findings were related to the testes such as degeneration, vacuolation and atrophy of seminiferous tubular epithelium found in mouse and dog. The clinical relevance of these findings has been addressed.

The mechanism for testicular findings in mice has been addressed in the carcinogenicity study and compares and contrasts this finding to the compound-related testicular alterations reported in the testes of dogs given tadalafil. The justification regarding the low relevance of the mice testicular findings is

acceptable. In mice, microscopic features of degeneration of seminiferous epithelium in the testes in both control and tadalafil-treated mice were similar in incidence and seem to be consistent with the commonly reported, age-related testicular degeneration in this strain and species. Therefore, as the Applicant states this finding is not attributed to administration of tadalafil.

In dogs, the exact mechanism for the tadalafil-related testicular alterations remains unclear. A mechanistic hypothesis to explain the underlying tadalafil-related testicular alteration reported in dogs has been provided. It is argued that the lesions observed are consistent with thermal or hypoxic injury due to pharmacological action and could be a species-specific effect. If testicular anatomical differences between man and dog are considered, there is a plausible explanation although unproven.

In addition the Applicant also refers to seminiferous tubule degeneration in dogs observed with vasodilator compounds such us terazosin, doxazosin and prazosin without adverse effects reported in humans for some of them. The human studies with tadalafil that have been conducted so far, do not provide further evidence of testicular toxicity. Although a small decrease was seen in sperm concentration in one study after a 6 months daily treatment with 10 mg, it is acknowledged that the magnitude of the decrease lies within the normal intraindividual variability, and that there is a lack of consistent findings in motility or morphology. Furthermore a replicate study with 20 mg did not show any effect on sperm at 6 months

Albeit the arguments presented, a further consideration of significant importance is the number of sperm cycles covered in the preclinical and clinical studies. The maximum number of sperm cycles covered in the 6- and12-month dog study was approximately 3 and 5, whereas in the 6-month clinical study in humans only about 2 sperm cycles were covered. Since the clinical study covers less than the minimum sperm cycles covered in the dog, the clinical study does not provide sufficient assurance for daily use in man for more than 6 months. The applicant has therefore agreed to perform a further study to investigate semen characteristics in humans given 20mg of tadalafil daily for 9 months. The testicular alterations (regression of the seminiferous tubular epithelium and the resulting decrease in spermatogenesis in some dogs) have also been reflected in the SPC

Decreases in platelet count were observed in a 1-year dog study. Additional information provided by the company did not reveal similar treatment-related haematology changes in rats or mice given tadalafil for up to 6 months. Furthermore, there have been no observations up to date of similar clinically significant, tadalafil-induced changes in neutrophil or platelet counts to date in over 4000 patients, including some patients treated with tadalafil for periods greater than 1 year. Therefore, the findings in dogs were considered to be clinically not relevant.

Vascular lesions were noted in rat studies with tadalafil and occurred in multiple organs. Supplementary information provided by the company reveal that vascular findings were also reported in rats given vehicle control or tadalafil. The vascular lesions observed in the rats are similar to those described in the literature (references are provided) with a number of spontaneous conditions, and are similar in incidence and severity across all dose groups, including controls. Therefore, vascular lesions noted in rats can be considered as not clinically relevant.

However in dogs, the observed vascular lesions seem to be compatible to Beagle Pain Syndrome (BPS), an idiopathic disease with higher incidence in some colonies of beagle dogs where lesions generally occur in multiple arteries. Data suggest that administration of high doses of tadalafil may have exacerbated underlying BPS in the Beagle colonies used for earlier studies. Vascular findings thought to be related to BPS have also been reported with another PDE5 inhibitor (sildenafil) in dogs. A class-effect cannot therefore be ruled out. In addition, a search of the clinical safety database did not result in any evidence of a vascular inflammatory adverse event and therefore this is not considered to be of any concern.

Decreased thymus weights and thymic lymphoid atrophy were observed in some dogs given tadalafil. These thymic alterations were either consistent with age-related involution, were similar in incidence and severity to spontaneous alterations in concurrent controls, or were secondary to stress or spontaneous inflammation. No compound-induced alterations occurred in lymphoid organs (thymus, spleen, lymph nodes, and Peyer's patches), bone marrow, or in peripheral absolute lymphocyte counts in mice, rats, or dogs given tadalafil. No tadalafil-induced effects suggestive of immunotoxic potential were observed in mice, rats, or dogs given tadalafil.

- Genotoxicity

Tadalafil can be considered as non-mutagenic as a result of the battery of *in vivo* and *in vitro* assays carried out. The human metabolite most relevant to the genotoxicity studies is the catechol metabolite IC711. Justification has been provided for the lack of a separate metabolite identification study after metabolic activation since exposure to the catechol metabolite (IC711) is expected in the *in vitro* genotoxicity studies conducted, following the *in vitro* metabolism of tadalafil using microsomes from rat, dog, mouse and human liver.

- Carcinogenicity

Liver tumours were reported in male mice and rats in the carcinogenicity studies. While there was an apparent minor numerical increase in the number of hepatocellular neoplasms in male rats treated with the high dose of tadalafil, this difference was not statistically significant, and is likely to represent an incidental variation. Tadalafil caused hepatocellular microsomal enzyme induction in both mice and rats, and it is possible that this could lead to an increased incidence of hepatocellular neoplasms. However, even if this mechanism were operable in the mice and rats, hepatic microsomal enzyme induction is a common non-genotoxic biologic effect associated with hepatocellular tumour formation in rodents and is not considered relevant to human cancer risk

- Reproduction Toxicity

The only male reproductive toxicity study provided was in the rat, which is not a species affected by the testicular toxicity.

Clinical aspects

Clinical pharmacology

Pharmacodynamics

Tadalafil primary pharmacology has been assessed in four studies using “populations models”.

Population models were developed in three Phase 2 studies (LVAC, LVBF and LVBG) in which co-precipitate tablets were used. In these studies, tadalafil was administered at dosages ranging from 2 mg to 100 mg.

The final model was developed in a Phase 3 trial (LVCE) using tadalafil market-image tablets up to 10 mg in an “as needed” dose regimen.

All population pharmacodynamic modelling was based on responses to the Sexual Encounter Profile (SEP) questionnaire and the International Index of Erectile Function (IIEF) questionnaire.

The general structural model was based on the pharmacologically relevant maximal drug effect (E_{max}) model describing a saturable drug response with increasing dose. The E_{max} model parameters of interest were dose for half-maximal effect (E_{50}) and E_{max}.

Patients were instructed to complete a SEP entry after each attempt at sexual intercourse. The SEP variable reflects the patient's acute response to drug treatment at the time of attempted sexual intercourse. Questions 2 and 3 are regarded as the most objective measures for drug effect: Question 2 inquires “Were you able to insert your penis into the partner’s vagina?”; Question 3 inquires, “Did your erection last long enough for you to complete intercourse with ejaculation?” (or “Did your erection last long enough for you to have successful intercourse?”).

The probability of a score of 1 ("yes") across all sexual attempts during a study interval was modelled.

The populations models predicted that an increase of the dose from 10 mg to 20 mg would increase the IIEF EF Domain score by 2.4 points and the relationships between tadalafil dose and combined SEP Question 2/Question 3 and the IIEF EF Domain was also predicted.

The tadalafil treatment effect in the combined SEP Question 2/Question 3 model was most appropriately described as a linear function of dose indicating that the maximal possible response was

not attained with a 10 mg tadalafil dose, since a continuously increasing response with increasing dose was predicted.

Patients with the most severe ED prior to treatment, represented by a baseline probability close to 0 (negligible chance of successful intercourse), benefited most from tadalafil therapy.

No specific formal pharmacodynamic studies with the usual laboratory models (Rigiscan) were performed except one study (LVBJ) intended to assess the responsiveness during the first hour after administration and 24 hours after administration. Further data from one additional study (N=45) has been provided which assessed the effect of 100 mg tadalafil (early research co-precipitate formulation) compared with placebo in improving erectile function in patients with mild to moderate erectile dysfunction (ED) as assessed by Rigiscan penile plethysmography during 36 minutes of visual sexual stimulation, 5 hours following dosing.

Regarding the secondary pharmacology of tadalafil, two studies were performed in order to assess the effects of tadalafil in visual function. No relevant findings in visual function were observed.

The effect of tadalafil on platelet aggregation, gastrointestinal or other possible pharmacological actions have not been investigated in formal pharmacodynamic studies.

Tadalafil at 20 mg may induce a blood pressure decrease, which is, in general, minor and not likely to be clinically relevant. This is referred to under "*Interaction Studies"*.

Pharmacokinetics

Absorption

Tadalafil is absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved approximately at a mean time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined. Tadalafil tmax is about 2 hours. Its mean volume of distribution is approximately 63 l.

The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. Tadalafil pharmacokinetics in healthy subjects is linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Metabolism

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform and several inactive metabolites have been identified in plasma, urine or faeces: the methylcatecol glucuronide that is the main circulating metabolite in plasma, the catechol glucuronide, two hydroxylated compounds, and the catechol derivate (in some subjects).

Excretion

Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

- Pharmacokinetics in special populations:

Tadalafil 10 mg was administered to elderly healthy subjects aged 65 to 78 years. The systemic exposure was higher in elderly subjects than in healthy subjects aged 19 to 45 years. This effect of age is not clinically significant.

Tadalafil 10 mg has been administered to subjects with mild (creatinine clearance 51 to 80 ml/min), moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal failure undergoing haemodialysis; and also in patients with mild and moderate hepatic impairment. Tadalafil has not been studied in subjects in patients diagnosed with severe hepatic dysfunction. Since there are no available data administering tadalafil 20 mg to patients with any degree of renal or hepatic impairment, the use of tadalafil 20 mg in patients with renal or hepatic impairment is not justified. Ten mg could be considered for these patients, as there is sufficient efficacy data to support some therapeutic effect at this dose.

The integrated pharmacokinetic analysis revealed that smokers had statistically significant shorter t½ values and smaller AUC and Cmax values compared to non-smokers.

Tadalafil has been studied in diabetic patients in a limited pharmacokinetic study. Although from a pharmacokinetic point of view this study is of little value, the existence of phase III data in diabetic patients give some reassurance that the small difference in exposure (19%) observed in the PK study is not clinically significant for this population.

No studies have been performed in children, but due to the therapeutic indication of the product, they are not necessary.

Interaction studies

Interaction studies have been performed to assess the pharmacodynamic and/or pharmacokinetic effects of tadalafil on several drugs or vice versa. A complete evaluation of potential pharmacodynamic and pharmacokinetic interactions has been performed both in healthy volunteers and in patients mainly diagnosed of cardiovascular diseases (hypertension).

Tadalafil has been studied with H_2 antagonists and antacids, with rifampicin, a specific CYP3A4-inducer and ketoconazole, a specific CYP3A4 inhibitor. No clinically relevant effects were observed in the antacid and H2 antagonist studies. However, rifampicin reduced the AUC for tadalafil. Ketoconazole showed inhibition of the systemic clearance of tadalafil clearly increasing the AUC for tadalafil.

Most interaction studies have been performed with tadalafil at a dose of 10 mg (studies for rifampicin, ketoconazole, midazolam, warfarin, among others). Only some pharmacology interaction studies are available with tadalafil at a dose of 20 mg: lovastatin, several angiotensin ATII receptor antagonists, amlodipine, tamsulosin and ethanol.

The possibility that tadalafil might be a mechanism-based inhibitor of CYP3A4 was investigated with the CYP3A4 probe substrates midazolam and lovastatin and with amlodipine that has inhibitory potency towards CYP3A4 (and also a weak reversible inhibitor for CYP2D6 and CYP2C9). No clinically relevant interactions were found for midazolam, lovastatine or amlodipine. For drugs that are CYP3A4 substrates, the absence of clinically relevant interactions for lovastatin, administered at the dose of 20 mg might be extrapolated to midazolam and other CYP3A4 substrates. However, the existence of clinically relevant drug interactions of the full dose (20 mg) of tadalafil cannot completely be ruled out.

The possibility of Pgp-mediated transport of tadalafil and possible effects of tadalafil on this transporter has been appropriately reflected in the SPC

The possibility of interactions between tadalafil and CYP1A2, CYP2C9, and CYP2D6 substrates was assessed with theophylline, warfarin and the β-blocker metoprolol, respectively. No clinically relevant effects were found in general in these interaction studies, although the theophylline study showed a statistically significant increase of heart rate in patients taking tadalafil (10mg) plus theophylline. A statement recommending caution when tadalafil is coadministered to theophylline has been included in the SPC.

No interaction studies have been conducted with tadalafil with protease inhibitors. The SPC does note the potential for protease inhibitors to increase the plasma concentration of tadalafil and a recommendation of caution regarding the co-administration of these drugs has been included in section 4.5.

Two studies were performed in order to assess the existence of pharmacological interactions between tadalafil and alcohol. Small and transient reductions in systolic and diastolic blood pressure occurred following both treatments. These changes were accompanied by compensatory increases in heart rate. For the main endpoint (maximum reduction in standing systolic blood pressure), the 95 % CI for the mean difference between the two treatments was completely contained within the predefined equivalence limits of –8 mmHg to +8 mmHg.

One study was performed in order to assess the effect between tadalafil and oral contraceptives. Co-administration of tadalafil increases systemic exposure to the ethinylestradiol component of the oral contraceptive. The data suggest that the primary effect of tadalafil is on the bioavailability of ethinylestradiol, with little effect on systemic plasma clearance of ethinylestradiol. This increase may be shared by other oral drugs, such as terbutaline and is mentioned in the SPC.

The cardiovascular profile of tadalafil appears similar to other agents belonging to the same therapeutic class. The decreasing effect in blood pressure has been correctly characterised when tadalafil is co-administered with nitrates. Three interaction studies with nitrates showed a marked reduction in blood pressure, therefore, the coadministration of tadalafil and nitrates is contraindicated.

The potential for tadalafil to increase the hypotensive effect of antihypertensive agents was also examined in six separate studies. Major antihypertensive classes were examined with a calcium channel blocker (amlodipine, 5 mg PO QD), an angiotensin-converting enzyme inhibitor (enalapril, 5 mg or 10 mg PO BID), a beta blocker (metoprolol SR, 50-200 mg PO QD), a thiazide diuretic (bendrofluazide, 2.5 mg or 5 mg PO QD), an angiotensin II receptor blocker (any type and dose or combination with other antihypertensive agents was acceptable) and an alpha 1A receptor blocker (tamsulosin, 0.4 mg PO QD). It is clear that tadalafil decreases the blood pressure in patients treated with AT II receptor antagonist agents. This decrease is not very pronounced but it cannot be excluded that it may be important for individual patients.

New analysis and data regarding the effect of tadalafil in blood pressure when antihypertensive medications are given simultaneously suggest that tadalafil may decrease blood pressure and those decreases may be more evident in patients receiving an antihypertensive treatment. Although this decrease is, in generally slight, tadalafil should be administered with caution to patients receiving antihypertensive medication. Cautionary advice has been included in the SPC on possible interactions of antihypertensive therapy and tadalafil.

Clinical efficacy

The clinical trials were performed according to GCP standards and agreed international ethical principles.

Dose response studies

Dose finding studies have explored doses ranging from 2 mg to 100 mg. All doses have shown differences to placebo. Although the 2.5 mg dose did not show efficacy so as to be considered an efficacious treatment for erectile dysfunction, it does show differences to placebo in its achievement of a Cmax (unbound concentration) about 8 times the IC50 after a single 2.5 mg oral dose. Nonetheless a dose-related effect was observed; 100 mg appeared to be the worst tolerated.

It is noted that dose-finding studies were performed using the same clinical subjective variables as those used in pivotal clinical trials.

All studies tested fixed doses in parallel groups. No dose titration studies have been performed trying to explore responses to higher doses in patients without adequate response to 10-20 mg.

Dose titration was performed in two long-term studies that were open label extensions of the efficacy controlled clinical trials. Doses of 5, 10, 25 and 50 mg (co-precipitate formulation) were used in one study, and doses of 5, 10, and 20 mg (market image formulation) were used in the other. Although in these studies the expected spontaneous trend is to achieve the higher dose if tolerated, at least one third of the patients remained on the 25 mg dose without increasing to 50 mg.

Although 5-mg, 10-mg, and 20-mg doses have not been directly compared within a single study, there have been two comparisons of 10 mg with 5 mg and two comparisons of 20 mg with 10 mg. Because the results of both sets of comparisons were consistent, these results are considered to be sufficient to establish a positive dose-response relationship in the range of 5 mg to 20 mg.

The doses of 10 and 20 mg (final formulation) were further tested in phase III trials.

Main studies (phase III trials)

Description of the studies

Six pivotal trials have been performed. In four of the six studies, a 20mg dose was used, including a study exclusively in patients with diabetes. The other two trials had the 10 mg dose as the highest tested dose.

Primary Placebo-Controlled Phase 3 Clinical Trials

Report code Number (location) of center(s)	Design	Number of Subjects Randomized With Age and Sex	Diagnosis Plus Criteria for Inclusion	Duration of Treatment	Test Product / Formulation / Dosage[b] / Regimen / Route of Administration	Criteria for Evaluation
H6D-MC-LVBN 19 centers	Double-blind, placebo-controlled, parallel	N=215 Ages≥18 Males	Mild to severe ED No nitrate therapy No unstable angina	12 weeks	IC351 Market Image 5mg, 10 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3
H6D-MC-LVCE 18 centers	Double-blind, placebo-controlled, parallel	N=308 Ages≥18 Males	Mild to severe ED No nitrate therapy No unstable angina	12 weeks	IC351 Market Image 2.5, 5 and 10 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3
H6D-MC-LVDJ[a] 25 centers, Canada	Double-blind, placebo-controlled, parallel	N=253 Ages ≥18 Males	Mild to severe ED No nitrate therapy No unstable angina	12 weeks	IC351 Market Image 10 mg, 20 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3
H6D-MC-LVCQ 4 centers, Australia	Double-blind, placebo-controlled, parallel	N=140 Ages ≥18 Males	Mild to severe ED No nitrate therapy No unstable angina	6 months; 3-month interim report submitted in the MAA	IC351 Market Image 20 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3
H6D-MC-LVCO[a] 8 centers, Taiwan	Double-blind, placebo-controlled, parallel	N=196 Ages ≥21 Males	Mild to severe ED No nitrate therapy No unstable angina	12 weeks	IC351 Market Image 10 mg, 20 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3
H6D-MC-LVBK (patients with diabetes mellitus) 18 centers, Spain	Double-blind, placebo-controlled, parallel	N=216 randomized Ages ≥18 Males	Patients with diabetes mellitus, mild to severe ED No nitrate therapy No unstable angina	12 weeks	IC351 Market Image 10 mg, 20 mg; PRN, oral	IIEF EF domain (Q1-Q5, Q15); SEP Q2,Q3

Abbreviations: ED = Erectile Dysfunction; IIEF = International Index of Erectile Function Questionnaire; PRN = 'as needed', Q = question; SEP = Sexual Encounter Profile; MAA = Marketing Authorisation Application.

a Samples were obtained for pharmacokinetic evaluation

b All PRN doses are taken 'as needed' up to once daily

All the pivotal trials incorporated a 4-week, treatment-free run-in period to establish baseline erectile function and sexual performance and efficacy was evaluated at 12 weeks (6 months in one study), as the change from the baseline assessment.

Patients were instructed to take the tadalafil dose on demand, at any time prior to anticipated sexual activity with the limit of a maximum frequency of one (1) dose per day. It seems that the dosing instructions were deliberately non-specific and that tadalafil could be taken without regard to specific timing relative to sexual activity and without regard to food or alcohol.

The study population were men in a stable monogamous relationship with a female partner and who reported at least a 3-month history of ED although most patients reported a history of at least 1 year duration. In relation to cardiovascular disease, patients were excluded if they were taking nitrates or suffered unstable cardiovascular disease including unstable angina, New York Heart Association (NYHA) Class 2 or greater congestive heart failure or uncontrolled hypertension.

Efficacy variables

The trials used three co-primary variables. All of them measured the erectile function as perceived by the patient, one over the course of the last 4 weeks (IIEF erectile domain) and the other two by means of two direct questions recorded immediately after the sexual attempt (SEP questions 2 and 3).

The use of these three variables as co-primary variables is considered satisfactory to provide an adequate demonstration of efficacy. The instruments of measure are the same as those used in previous submissions with other products to treat ED.

- The IIEF (International Index of erectile function) is a self-administered questionnaire, validated in over 30 languages and that is commonly used to assess the effect of ED therapy and to judge the severity of the disease. It assesses patients opinion on his erectile function over the prior 4 weeks.

  The IIEF has 15 questions comprising five domains, one of them devoted to the erectile function, as assessed by six questions that ask whether the patient can obtain erections during sexual activity, can penetrate his partner, and can maintain an erection after penetrating his partner. The domain also asks the patient to assess his difficulty in achieving erections and his confidence in his ability to achieve and maintain erections. The possible total score ranges from 1 to 30.

- The Sexual Encounter Profile (SEP) diary consists of a one-page questionnaire that is completed by the patient shortly after each sexual attempt. In some studies identical questionnaires were provided to partners and they were instructed to complete independently, a separate SEP questionnaire. The SEP has five questions. Answers are scored as "Yes" or "No".

1. Were you able to achieve at least some erection (some enlargement of the penis)?
2. Were you able to insert your penis into the partner's vagina?
3. Did your erection last long enough for you to have successful intercourse?
4. Were you satisfied with the hardness of your erection?
5. Were you satisfied overall with this sexual experience?

Questions 3 and 4 in the Overall Satisfaction Domain of the IIEF were secondary variables in primary efficacy studies. IIEF Question 3 asked patients, "When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?" IIEF Question 4 asked patients, "During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?"

Statistical analysis

ANOVA models were used to evaluate change-from-baseline efficacy variables. These models included terms for baseline value of the efficacy variable, treatment group, pooled site, and the baseline-by-treatment-group interaction (if significant, $p<0.10$). For primary efficacy analyses, p-values were adjusted for multiplicity as multiple tadalafil doses were administered in most studies and multiple comparisons were made.

Study populations

The study population were men in a stable monogamous relationship with a female partner and who reported at least a 3-month history of ED although most patients reported a history of at least 1 year duration. ED was of psychogenic, mixed and organic etiology, with a predominant diagnosis of the two last categories. This population may be considered representative of the target population also in terms of age, concomitant hypertension or diabetes, alcohol or smoking.

Elderly patients were also included in all the efficacy clinical trials. Efficacy in patients aged over 65 years was evaluated with an integrated analysis across the five primary efficacy studies.

Patients suffering from ED because of spinal cord injuries or other neurological diseases as well as prostatectomized patients or patients after pelvic surgery or trauma have been excluded or are poorly represented in clinical trials. As the efficacy in these patients is unknown, an appropriate statement has been included in the SPC.

Efficacy results

Summary of Change from Baseline in IIEF EF Domain Scores (All Randomized Patients, Studies LVCO, LVCQ, and LVDJ)

	ALL		Placebo		IC351 10mg		IC351 20mg		
	BASE	END	CHG	END	CHG	P	END	CHG	P
IIEF Domains									
Erectile Function									
LVCO	15.7	18.1	2.6	22.6	8.1	<.001	25.0	8.0	<.001
LVCQ	15.4	13.0	-1.3				23.7	7.7	<.001
LVDJ	15.0	14.5	-0.9	21.2	6.6	<.001	23.3	8.0	<.001

BASE = Mean over all patients at baseline (Visit 2)
END = Mean within treatment group at endpoint
CHG = Mean within treatment group of change from baseline to endpoint

Summary of Change from Baseline in SEP Question 2 Scores (All Randomized Patients, Studies LVCO, LVCQ, and LVDJ)

	ALL		Placebo		IC351 10mg		IC351 20mg		
	BASE	END	CHG	END	CHG	P	END	CHG	P
Patient SEP Questions									
2. Insert Penis into Vagina									
LVCO	45.7	54.5	9.5	76.9	34.5	<.001	84.9	35.3	<.001
LVCQ	53.0	42.4	-7.2				81.3	26.5	<.001
LVDJ	52.7	45.3	-6.4	72.5	21.3	<.001	76.0	21.3	<.001

BASE = Mean over all patients at baseline (Visit 2)
END = Mean within treatment group at endpoint
CHG = Mean within treatment group of change from baseline to endpoint.

Summary of Change from Baseline SEP Question 3 Scores (All Randomized Patients, Studies LVCO, LVCQ, and LVDJ)

	ALL		Placebo		IC351 10mg		IC351 20mg		
	BASE	END	CHG	END	CHG	P	END	CHG	P
Patient SEP Questions									
3. Successful Intercourse									
LVCO	26.2	42.8	14.7	70.0	47.9	<.001	78.0	49.7	<.001
LVCQ	30.8	26.2	0.4				74.1	40.7	<.001
LVDJ	27.9	31.9	4.9	56.7	32.8	<.001	61.5	29.0	<.001

BASE = Mean over all patients at baseline (Visit 2)
END = Mean within treatment group at endpoint
CHG = Mean within treatment group of change from baseline to endpoint.
For each variable, population summarized consists of patients having both baseline and post-baseline data

The superiority of tadalafil 20 mg versus placebo was statistically significant and clinically meaningful in all three co-primary variables and in all the trials. In all studies, doses of 2.5 mg, 10 mg, and 20 mg tadalfil significantly improved responses to SEP Question 2. The 5 mg dose significantly improved the response to SEP Question 2 in Study LVCE. In all studies, all doses significantly improved patients' ability to maintain their erection for successful intercourse compared with placebo. The mean improvement for all doses was at least 19%.

Tadalafil 20 mg was consequently found to be superior to placebo in all-secondary variables in all the studies (global assessment question, rest of the Sexual Encounter Profile questions, IIEF Intercourse Satisfaction and Overall Satisfaction Domains).

Treatment with tadalafil 5 mg, 10 mg, and 20 mg provided significant improvement in the Overall Satisfaction Domain in all studies. All doses of tadalafil showed statistically significant improvement

in IIEF Question 3 compared with placebo in all studies. In all studies, 2.5mg, 10mg, and 20 mg tadalafil demonstrated a statistically significant improvement in the IIEF Question 4 compared with placebo. The 5 mg dose of tadalafil significantly improved the response to Question 4 in Study LVCE but not in Study LVBN (p=0.066).

Efficacy in patients aged over 65 years was evaluated with an integrated analysis across the five primary efficacy studies. As assessed by all primary variables (IIEF EF Domain, SEP Question 2, and SEP Question 3), tadalafil significantly improved erectile function in a similar magnitude to that in younger patients.

A pooled analysis of responses to 10 mg and 20 mg based on all phase III trials shows statistically significant differences between 10 and 20 mg. Albeit the magnitude of this difference is rather marginal, a similar safety profile has been observed for both doses.

The clinical relevance of the effect is also shown by the analysis of responders; taking as a responder the patients who achieved normal erectile function with treatment (patients who reach a score of 26 or greater). Across all studies and severities, 58.6% of patients who received 20mg tadalafil improved to the no-ED category (normal) at endpoint, compared with 39.7% for the 10mg tadalafil patient group and 10.9% for the placebo patient group.

With respect to the choice of the starting dose, 20 mg or 10 mg, the applicant was of the view that the starting dose should be 20 mg and doses may be subsequently lowered based on individual response and tolerability. It was argued that because failure of ED therapy can worsen the psychological aspects of ED, patients should be treated initially with the most effective dose that is safe and well tolerated. This method of treatment of titrating downwards has not been the rule with previously accepted PDE5 inhibitors and is not necessarily the optimal strategy taking into account that only a few patients are expected to obtain more benefit from the 20 mg dose than with the 10 mg dose. Therefore a starting dose of 10 mg was finally agreed.

Specific studies intended to assess the period of responsiveness, to discriminate clearly the period of maximum responsiveness with tadalafil 20mg, were performed. These studies suggest a window that may be confirmed by the data obtained from clinical trials. Tadalafil 20 mg shows an effect at 30 minutes post dose. With respect to the end of the period of responsiveness, there is evidence from one clinical trial of an effect at 24 and 36 hours post dose. In addition, efficacy at 24 hours is also supported by a pharmacodynamic study (Rigiscan).

Data from the clinical trials, show that a substantial number of patients attempted sexual intercourse about 30 minutes after dosing, and difference from placebo seems to be confirmed. However, with respect to the end of the period, there were not enough observations at specific time-points post 14 hours to statistically demonstrate efficacy. The Posology indicated in the SPC recommends a window of opportunity between 30 minutes and 12 hours.

There are insufficient safety data to allow the daily doses use of tadalafil as a chronic treatment. Since daily use could be seen as an attractive regimen to some patients, a clear sentence discouraging the chronic daily dosing has also been included in the posology section.

- Comparative efficacy

The comparative efficacy with sildenafil 50 and 100 mg is unclear. Three active comparator trials are submitted one of them with characteristics of a pilot study.

In the first well-designed placebo controlled trial, tadalafil 5 or 10 mg appeared superior to placebo but it did not reach the non-inferiority margin as compared to sildenafil 50 and 100 mg.

In another study, tadalafil at the maximum 20 mg is compared to sildenafil 50 mg and 100 mg, but several deficiencies in the design preclude the acceptance of non-inferiority.

- As many as half of the patients suffered from mild ED and it seems that there were patients included that did not suffer from erectile dysfunction according to the baseline IIEF scores. Scores of 27 and 30 are the upper limit of the basal IIEF scores (normal 26-30).

- Sildenafil (and tadalafil) was recommended to be taken 1-5 hours before sexual activity. However SPC recommends that Sildenafil should be taken one hour before sexual activity, based on PK/PD and clinical considerations. A window of 5 hours is considered too large and may have resulted in a lack of efficacy with sildenafil.

The comparison of the tadalafil efficacy results to those historically shown in the sildenafil trials is also very difficult because the patient populations and trial design are different. It is noted that in most studies the tadalafil population excluded those with prior lack of response to sildenafil and therefore, higher rates of response may be expected from tadalafil trials. Also, some relevant groups of patients such as those who had radical prostatectomy (or other pelvic surgery) or spinal cord injury, with expected lower rates of success, have been excluded from tadalafil studies, while included in sildenafil trials**.**

Therefore, the comparative efficacy of tadalafil versus sildenafil is unknown. However, considering that this is a symptomatic treatment and that the assessment of individual responses to both products is feasible, it is considered acceptable to base the approval of efficacy only in comparison to placebo.

- Long term efficacy

After reviewing results from the 6 months trial (LVCQ), there is no evidence of the development of tolerance in efficacy.

Clinical studies in special populations

The fourth pivotal trial (LVBK) was performed in diabetics. Tadalafil 10 mg and 20 mg showed consistent efficacy versus placebo. As supplementary information, a subgroup-analysis on the limited number of diabetic patients included in the other three efficacy trials, also demonstrate efficacy in these patients.

Clinical safety

Safety data are analysed from the following groups of studies:

a) Placebo-controlled clinical studies : LVBN, LVCE, LVDJ, LVCQ (3-month interim data), LVCO, and LVBK. All these studies used the final formulation but at different dosages with a substantial proportion of patients using dosages lower than 20 mg.
b) Open-Label, Long-Term Safety Studies : Studies LVBD and LVBL
c) Sildenafil controlled clinical studies
d) Clinical Pharmacology Studies.
e) The rest of the phase II and III studies are only analysed individually and their data are not integrated in any global analysis.

For all completed studies, the last patient visit date was 19 April 2001. For all ongoing studies, serious adverse events are reported up to 02 April 2001 and deaths are reported up to 28 May 2001. However the cut-off date for analysis of the long-term studies is reported to be 1 March 2001.

It is noted that most of the patients received doses inferior to the 20 mg.

Patient exposure

A number of 949 patients were randomized to receive tadalafil in pivotal placebo controlled phase 3 studies LVBN, LVCE, LVDJ, LVCQ (3-month interim data), LVCO, and LVBK (patients with diabetes mellitus) and they are the subject of an integrated analysis, which is considered the primary placebo-controlled database.

Due to the use of doses of 2.5 mg, 5 mg, 10 mg, and 20 mg, only 330 of them were randomized to receive 20 mg. However only 311 out of these 330 really received treatment. The mean length of study participation was approximately 90 days and patients took a mean of 25 to 30 doses in different treatment groups during the studies, which translated to a mean of approximately 2 doses per week.

Therefore this primary data base accounts only for 311 patients receiving 20 mg doses. This contrasts with the number of 3,571 patients and healthy volunteers that have received the product during the clinical development.

Long-term data (> 3 months) were only available from open label studies, as follow-up of patients after their participation in clinical trials (open label study LVBL), at the time of the original submission. Subsequently some additional data became available: data from 111 subjects included in a 6-months placebo controlled trial intended to assess the testicular safety and also the final 6 months report of trial LVCQ, where 93 patients received 20 mg tadalafil.

At the time of the initial submission, up to 557 have received 20 mg up to 6 months and 88 patients up to a year (cut-off date 1 March 2001). Some information can be also obtained from another open label trial (LVBD) where the recommended 20 mg dose as the market image formulation, or its equivalent dose or higher (25 mg, 50 mg) as the co-precipitate formulation, was taken by 163 patients for ≥6 months, and by 143 patients for ≥12 months).

Frequent adverse events

In placebo controlled efficacy trials, 66.7 % of patients receiving the 20 mg dose experienced a treatment emergent adverse event, compared to 54.3 % with 10 mg and 47.8 % with placebo.

Headache, dyspepsia, back pain, myalgia, rhinitis (nasal congestion), and vasodilatation (flushing) occurred in more than 2% of the tadalafil-treated patients and were more frequent than in the placebo-treated patients. These events were generally less frequent for the 2.5mg and 5mg dose groups and varied in incidence between studies. All these adverse reactions are known to happen with the other available PDE 5 inhibitors. The SPC includes the frequencies of occurrence and severities of the pool of doses 10-20mg.

Headache is reported in placebo controlled clinical trials by 14.5 % of the patients (10-20 mg) versus 5.5% of placebo patients and more frequently in healthy volunteers. The duration of the headache related to tadalafil seems to be around 3 to 8 hours and no clear increase with increasing doses is shown.

Headache is a common adverse reaction of tadalafil, which is most probably related to its mechanism of action. Headaches may be severe and become a cause for discontinuation. Most cases appear with the first dose of treatment and their incidence seems to decrease with the continued dosing. Data analyses perfomed show that both, prevalence of headaches and incidence of the first headache, decrease over time in Phase 3 studies.

Dyspepsia is possibly related to the relaxation of lower esophageal smooth muscle tone by inhibition of PDE5. Dyspepsia is reported in placebo-controlled clinical trials by 12.3 % of the patients (10-20 mg) versus 1.9% of placebo patients.

Back pain and myalgia was observed to be a frequent adverse event of unknown origin. It is not related to physical activity; on the contrary, it was more frequent in healthy volunteers in clinical pharmacology studies. From the pivotal placebo-controlled trials, the reported incidence after 10-20mg is 6.5% suffering back pain and 5.7% myalgia, versus 4.2% and 1.9% respectively with placebo. In healthy volunteers/patients included in clinical pharmacology studies, incidence of back pain was 28.2% versus 6.2% with placebo and the incidence of myalgia was 22.6% versus 5.5% with placebo. In patients with moderate renal impairment, 4 out of 6 patients reported back pain.

Although in the sildenafil trials some cases of back pain were reported, the incidence of reported back pain is higher with tadalafil in comparison with sidenafil. Around a 16% of the reported back pain were qualified as severe and it has been also the cause of discontinuation in some subjects. However it is difficult to definitively conclude about a possibly higher incidence or duration than with the other PDE inhibitor, sildenafil, that has a shorter duration of action.

There are no signs of an inflammatory or myopathic mechanism involved in these adverse events (no changes in CK, ESR or other laboratory markers). The applicant proposes a hypothesis based on vasodilation and muscular vessel congestion, suggested by the fact that it seems to be more frequent in volunteers resting in bed and without activity. It is not known if the long duration of action may have a role in the appearance of this effect.

Rhinitis/ nasal congestion and Vasodilation (flushing) were also reported to be associated with treatment and again they are not unexpected according to the adverse reactions profile of previous PDE inhibitors (eg sildenafil). The incidence at 10-20 mg in placebo-controlled studies is around 4.3% and 4.1% for nasal congestion and flushing respectively

Serious adverse events and deaths

The applicant as related to tadalafil has considered no deaths or serious adverse events. Those cases considered by investigators as possibly related are cardiovascular or cerebrovascular accidents that may also be explained by underlying diseases and, albeit from very limited data, there is no suggestion for an unexpected increase for these events in this high-risk population.

Laboratory findings

Haematology laboratory was assessed because of two cases of idiosyncratic neutropenia and thrombocytopenia that were observed in two female dogs in the toxicology program. No cases appeared in the clinical program. Two cases of clinically significant cases of neutropenia were detected but alternative causes were more plausible than tadalafil (recovery without stopping long term treatment or a Hodgkin's disease). It has to be recognised however that the number of patients is limited and that some of them have received doses lower than the finally proposed dose of 10 mg. Therefore this should also be part of the post marketing surveillance.

Safety in special populations

The clinical safety and lack of interactions in diabetic patients was also addressed during the evaluation. Although the specific study LVBK does not suggest changes in glucose control or a different profile of clinical safety than in non diabetics, the population size receiving 20 mg is not completely reassuring; 72 patients in the specific study LVBK plus 43 patients included in the other 3 pivotal trials. Taking into account the lack of specific PD/PK studies in diabetics (e.g. absence of interaction study with oral hypoglycemic products, studies on blood pressure decrease), an appropriate statement of this lack of specific interaction studies with antidiabetic agents has been included in the SPC.

In the group of patients >75 years, the percentage of tadalafil subjects experiencing any emergent adverse events was observed to be much higher than in the corresponding placebo, unlike in other age groups. This is very likely to be due to the very low percentage of adverse events in the placebo group, possibly related to the very low numbers in that age groups. The lack of patients above 75 years of age does not allow a satisfactory assessment of the safety profile of tadalafil in this patient population. However, taking into account the proposed restrictions in the SPC for patients with renal impairment and other disease conditions, data do not suggest the need for specific warnings based solely on the age.

Comparative safety

In spite of the submission of three studies controlled versus sildenafil, due to the limited sample size it cannot be concluded that tadalafil was better tolerated than sildenafil.

The only comparative study where tadalafil 20 mg is compared to sildenafil provides limited information about the more common side effects of both products. The study was double blind by using encapsulated tablets of both products and there is no suggestion of an increased frequency of the common side effects.

Similarly to what has been concluded in regard to comparative efficacy, there is not enough data to conclude on comparative safety. However, due to the nature of the symptomatic treatment and the nature of the so far expected adverse events, this may be considered acceptable.

Other safety considerations

Testicular toxicity on the long-term treatment has been a point for concern with this product, due to animal experiments that have shown testicular alterations. Clinical trials have been designed to take the product on demand and therefore, only one study (LVCZ) provides safety data of the daily use of 20 mg tadalafil. This study, intended to assess the effects on spermatogenesis, included 111 patients treated daily during 6 months. A few additional patients received different doses of tadalafil during 5 days per week in phase III 12-week trials (n=28) and in the open label 6 months trial LVBL (n=32). All together, there are insufficient patients to assess the safety profile of 20 mg of tadalafil in chronic daily use. Furthermore the database is not in compliance with the ICH recommended exposures to assess clinical safety in chronic daily use.

Therefore the currently available human studies do not provide evidence of testicular toxicity. Although a small decrease was seen in sperm concentration in one study after a 6 months daily treatment with 10 mg, it is acknowledged that the magnitude of the decrease is within the normal intraindividual variability, that there is a lack of consistent findings in motility or morphology and that a replicate study with 20 mg daily did not show any effect on sperm at 6 months.

However, the possibility of toxicity following long-term daily dosing exposure and the effect of tadalafil on human semen will be further investigated in a further long term study of 9 month duration, which the applicant has undertaken to carry out post-authorisation. (The currently available data do not allow the use of tadalafil as a chronic daily treatment and daily continued use is strongly discouraged in the SPC).

As with other PDE5 inhibitors there is a potential for decreasing the blood pressure, which might be of major concern in patients already taking antihypertensive products. The hypotensive effect of tadalafil seems modest but the submitted studies and the monitoring performed do not suggest that it does not exist. Clinical pharmacology studies with intensive monitoring are the most appropriate sources of information to quantify the magnitude of the effect; and in these studies, tadalafil was associated with a higher percentage of potentially clinically significant decreases in blood pressure compared to that of placebo. The potential of tadalafil to induce such decreases in blood pressure is inferior to that of nitrates and other antihypertensive products. An appropriate sentence recognising the low (but existing) potential for decreasing blood pressure has been included in section 5.1 of the SPC.

Tadalafil decreases the blood pressure in patients treated with AT II receptor antagonist agents. This decrease is not very pronounced but it is important for individual patients. Cautionary advice has been included in the SPC on possible interactions of antihypertensive therapy and tadalafil.

Analysis of adverse events potentially related to blood pressure decreases in clinical studies (syncopes, shock, hypotension, postural hypotension,dizzinness) do not suggest any relevant effects of tadalafil. However in spite of the limitations to assess causality, some cases of postural hypotension have been reported with tadalafil. This information has been included in the SPC.

Pooled data from studies using 10 and 20mg doses of tadalafil have shown that around 10% of patients have evidence of ischemic cardiac disease. A variety of other cardiovascular antecedents (some of them of little relevance) account for another 10%. The percentage of ischemic heart diseases, cerebrovascular antecedents or clinically relevant cardiovascular underlying disorders, although modest, allow assessment of the safety profile. It is borne in mind that as with other products for the erectile dysfunction, the SPC does not recommend treatment of patients whose underlying cardiovascular condition is so severe and unstable that the sexual activity itself is unadvisable. Nevertheless, cardiovascular safety does not seem to be a major source of concern provided that at-risk patients excluded from clinical trials are considered as contraindications as stated in the SPC.

In tadalafil-treated patients, the incidence rates of cardiovascular events were comparable between patients who were treated with concomitant antihypertensive medications and patients who were not. Most cardiovascular events were infrequent (<1%). In the overall safety database, no differences were observed in the rate of myocardial infarctions adjusted to 100 man-years compared to patients who received placebo.

However, there is still some concern regarding the safety of tadalafil in patients taking concomitant antihypertensive medications, and therefore appropriate information on the potential effect on blood pressure, also in addition to antihypertensive treatment, is included in the SPC. The applicant has undertaken to conduct a Post marketing Surveillance Study in which the cardiovascular risk in real use conditions will also be assessed. The protocol will be submitted and assessed by the CPMP.

Spontaneous erections have been reported, sometimes painful or uncomfortable. Although none of them were of a duration long enough to qualify as a priapism a cautionary statement has been included in the SPC.

OVERALL CONCLUSIONS, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality

The important quality characteristics of the active substance are well defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic for this kind of medicinal products. The specifications and batch analytical results indicate a consistent product with a uniform clinical performance from batch to batch. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Preclinical pharmacology and toxicology

The preclinical studies have adequately characterised the pharmacology and toxicology of the compound. The pharmacological studies performed have provided information on the mechanism of action and expected effects. Safety pharmacology studies performed do not suggest relevant adverse events.

Overall, the most important concern relates to the testicular findings in dogs after repeated administration of tadalafil that consisted of degeneration, vacuolation and atrophy of seminiferous tubular epithelium. Taking into account that these findings may also apply to humans an additional clinical study will be conducted post authorisation. These pre-clinical and clinical testicular findings have been appropriately addressed in the SPC.

Efficacy

The efficacy of tadalafil at 10 and 20mg doses has been adequately demonstrated. The 20 mg has not been proven substantially more efficacious than 10 mg (which is clearly better than placebo). The results of analyses from pooled trials and by post-hoc responder analyses suggest a marginally better effect of the 20mg dose although no dose titration studies are available exploring the response to higher doses in those patients who failed to respond to 10mg. Therefore a starting dose of 10mg was discussed and agreed by the CPMP and applicant.

The agreed posology recommends that tadalafil “can be taken up to 12 hours and as early as 30 minutes prior to sexual activity”. The maximum recommended dosing frequency is once per day and daily use of tadalafil is strongly discouraged.

There is no experience in patients with either liver or kidney impairment and, in both cases, exposure to tadalafil is increased. A starting dose of 10mg has been agreed for these patient populations.

Most of the interaction trials were carried out at the chosen dose of 10 mg.

Safety

The most frequently reported adverse events associated with tadalafil were headache, dyspepsia, back pain, myalgia, and flushing and nasal congestion. Subgroup analyses showed no difference in adverse events for patients taking tadalafil in patients >65 years of age, patients with diabetes mellitus, patients with hypertension, and patients taking concomitant antihypertensive medications.

Overall discontinuations due to adverse events in tadalafil - treated patients were low and not statistically different from placebo-treated patients. The overall mortality and rate of cardiovascular events do not reveal relevant differences. So far the only aspect that is of concern is related with the pre-clinical findings of testicular toxicity.

With the appropriate cautions/contraindications that have been mentioned in the SPC, the cardiovascular safety profile of tadalafil appears favourable. However, some mechanism of action related vasodilating effect is to be expected. It is shown that tadalafil further decreases blood pressure in patients treated with some antihypertensive substances (i.e. AT II receptor antagonists) Even if the decrease seems minor it cannot be excluded that it is important for individual patients. This possibility cannot be completely excluded when infrequent cardiovascular events in patients on antihypertensive therapy (and tadalafil or placebo) are considered. In this respect, the Company has undertaken to

conduct a posmarketing observational study (prescription event monitoring) similar to that being conducted with sildenafil.

Although it has been shown that there are no signs of testicular toxicity in patients treated with the proposed 20 mg dose (daily for six months), further reassurance is required. A study investigating the characteristics of human semen over a period of 9 months has been proposed and will be undertaken by the applicant post-authorisation.

Benefit/risk assessment

Cialis (tadalafil) is a member of the group of PDE-5 inhibitors intended to treat erectile dysfunction.

The main clinical differential characteristic of tadalafil appears to be its long half-life (around 17.5 hours) that suggests a longer therapeutic windows (time before the anticipated sexual activity during which the drug can be taken). This can be considered, at least in some instances, a desirable feature but it can be speculated that it may also result in specific disadvantages.

A concern on testicular toxicity has been raised based on the finding on tadalafil related testicular alterations in dogs. Results from two 6-month studies in volunteers suggest that this effect is unlikely in humans. A further study in humans to study the characteristics of semen has been proposed by the applicant and will be carried out post-authorisation.

As a summary, the benefit-risk balance for CIALIS can be considered positive.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Cialis in the treatment of erectile dysfunction was favourable and therefore recommended the granting of the marketing authorisation.