European Medicines Agency
Evaluation of Medicines for Human Use

London, 26 April 2007
Product Name: Cialis
Procedure No: **EMEA/H/C/000436/X/26-27**

SCIENTIFIC DISCUSSION

1 INTRODUCTION

Lilly ICOS Limited has submitted an application through the Centralised Procedure for Cialis film-coated tablet containing 2.5 mg and 5 mg of the active substance tadalafil.

The application is an extension of the existing Cialis 10 mg and 20 mg film-coated tablets (EU/1/02/237/001)- (EU/1/02/237/002-005) approved in November 2002 in accordance with Article 8.3 (i) of Directive 2001/83/EC.

As an alternative, the applicant applied for a new regimen: the new strengths (2, 5 mg and 5 mg) would be taken once daily as opposed to the current approved as-needed regimen (10 mg and 20 mg) used in the general population of patients with erectile dysfunction.

The active substance, tadalafil, is a potent selective, reversible inhibitor of phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of phosphodiesterase type 5 (PDE5), produces an increase of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. The result of this process is a smooth muscle relaxation and inflow of blood flow into the penile tissues, thereby producing erection. Tadalafil has no effect in the absence of sexual stimulation.

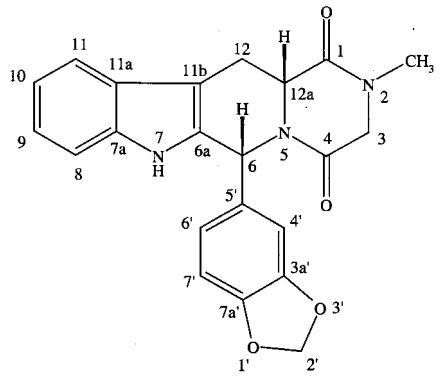
The finished product is formulated as film-coated tablets; the composition, packaging material, manufacturing process, specifications and stability are practically the same as the existing Cialis tablets.

2 Quality aspects

Introduction

Active Substance

The active substance tadalafil has already been approved for Cialis 10 mg and 20 mg.



The company refers to the currently approved dossier for Cialis 10 mg and 20 mg for all quality information related to tadalafil. No changes are required or provided to support the new 2.5 mg and 5 mg tablets strengths. Therefore the information has not been repeated.

Medicinal Product

- Pharmaceutical Development

The objective was to obtain tablets with an absorption rate allowing a rapid onset of action, with good stability properties, and of reproducible quality at commercial scale.

Studies carried out on the active substance showed that : thermodynamically stable, crystalline, non-hygroscopic and micronised tadalafil is incorporated into a wet granulation to consistently produce tablets with good homogeneity and the desired dissolution characteristics.

As the in vivo absorption of Class 2 drugs (low solubility and high permeability) is typically dissolution rate-limited, the impact of the particle size of tadalafil was investigated and micronised tadalafil was retained. Also, bioavailability studies, demonstrated that Tadalafil 2.5, 5, 10, and 20 mg Tablets are bioequivalent. Therefore the approved particle size specification for Tadalafil 10 and 20 mg Tablets is also applicable to 2.5 and 5 mg tablets. It was demonstrated that the crystalline form remained unchanged after the tablet manufacturing process.

Excipients used for the 2.5 and 5 mg tablets are identical to those used for the approved tablets: combination of lactose monohydrate and spray dried lactose monohydrate to promote a rapid dissolution; hydroxypropylcellulose (binder); croscarmellose sodium (disintegration agent), laurisulfate (wetting agent) and magnesium stearate (lubricant). Sufficient data are provided for the excipients (compendial or non-compendial) used in the core and the coating mixture of the tablets.

The formulation development showed that the combination of ingredients consistently produce a free-flowing, compressible, and easily wetted material, as well as tablets with low friability, acceptable hardness, and rapid disintegration.

All formulas for the 2.5, 5, 10, and 20 mg core-tablets are qualitatively identical and in percentage quantitatively very similar, with a concomitant adjustment of lactose monohydrate and magnesium stearate.The coating has minimal impact on the dissolution of tadalafil from the tablets.

The manufacturing process is based upon the process approved for Cialis 10 mg and 20 mg. The process is robust, reproducible and ensures the production of homogeneous and bioavailable tablets containing 2.5 and 5 mg of tadalafil.

The packaging materials are the same as those approved for Cialis 10 mg and 20 mg i.e blister made of PVC/PE/Aclar with PVC in contact with the product.

As a conclusion, the pharmaceutical development of the drug product is the same as Cialis 10 and 20 mg and has been sufficiently described. The justifications for the choice of the excipients, packaging material, and manufacturing process are acceptable.

- Adventitious Agents

None of the ingredients used is neither of ruminant nor human origin with the exception of lactose. The supplier of lactose certifies it is in compliance with TSE Directive 1999/82 EEC and the Public Statement EMEA/CPMP/571/02. It is excluded from the scope of "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agent via Human and Veterinary Medicinal Products."EMEA/410/01 rev 2 since the milk is sourced from healthy animals and in the same conditions as milk collected for human consumption. The current scientific knowledge is that materials derived from milk are unlikely to present any risk of TSE contamination.

- Manufacture of the Product

The manufacturing process for the 2.5 and 5 mg tablets is adequately described and consists of: high shear wet granulation, wet milling, drying, dry milling, blending, compression, coating/polishing.

The manufacturing process and in-process controls (thickness, friability, hardness, tablet weight and disintegration) for 2.5 and 5 mg tablets are identical to those approved for the existing tablets with the

following exception: reduced cone mill screen size used in the dry sizing step for the 2.5 mg granulation. The applicant has committed to complete the validation process at both manufacturing sites prior to commercial launch. This is acceptable.

- Product Specification

The proposed specification is identical to the one approved for the approved tablets, except for the physical appearance and the content of water that is not performed and justified. Specification at release and end of shelf-life includes: identification, assay, uniformity of content, related substances, appearance, microbial quality, identification of colorants, dissolution. The impurity profile for the 2.5 mg and 5 mg remains the same as for 10 and 20 mg tablets; no new impurities have been detected.

Analytical procedures for the 2.5 and 5 mg tablets are similar to those previously approved for the 10 and 20 mg tablets apart from adjustments allowing analysis of the lower strengths. The methodology remains essentially unchanged. Validation of those analytical procedures has been satisfactorily conducted in accordance with ICH guidelines.

Satisfactory batch analyses of 3 lots of each strength 2.5 mg and 5 mg have been provided. Data demonstrate that the proposed manufacturing process is adequately controlled, and that the quality of the tablets manufactured for clinical trials, primary stability, and validation are comparable.

- Stability of the Product

Primary stability studies have been carried out under ICH conditions, and using the commercial packaging on: 3 pilot batches of 2.5 mg (24 months at 30ºC/65% RH, 6 months at 40ºC/75% RH and supporting data for 1 batch, 60 months at 25ºC/60% RH) and 3 commercial batches of 5 mg (36 months at 25ºC/60% RH, 6 months at 40ºC/75% RH and supporting data for 1 batch, 36 months at 30ºC/70% RH). No significant trend of change could be observed at any of the storage conditions even after stress testing (such as heat, moisture, photostability). Based on the data, a shelf-life of 3 years can be granted as for the existing tablets.

The applicant has committed to perform stability studies on commercial batches for 2.5 mg tablets and to submit the results when available.

Discussion on chemical, pharmaceutical and biological aspects

Cialis 2.5 mg and 5 mg film-coated tablets have been developed based on the already authorized strengths. The composition of the two new strengths is qualitatively similar to the existing strengths.

Bioavailability studies, demonstrated that Tadalafil 2.5, 5, 10, and 20 mg Tablets are bioequivalent.

The results of test carried out indicate satisfactory consistency and uniformity of product quality characteristics, and these in turn lead to the conclusion that the new strengths should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant provided a Letter of Undertaking and committed to resolve it as Follow-Up Measure after the opinion, within an agreed timeframe.

3 Non-clinical aspects

Introduction

Pharmacodynamic, pharmacokinetic, and toxicology studies with tadalafil PDE5 inhibitor were performed and submitted to support the original marketing application of tadalafil, 10 and 20 mg taken as needed for the treatment of erectile dysfunction (ED).

Within this extension application (2.5 and 5 mg strengths used in a new dosage regimen), no additional non clinical studies were conducted. However, a comparison of the safety for doses administered in repeat-dose toxicology studies versus clinical steady-state exposure at the proposed 5mg tadalafil dose was made and an updated environmental risk assessment (ERA) was submitted.

- **Table 1 Comparison of Margins of Safety (Based on AUC) to Tadalafil in Rat, Dog, and Human**

Species/Dose	AUC_{0-24hr} (ng•hr/mL)		Margin of Safety[a] (based on unbound tadalafil)	
	Male	Female	Male	Female
Human[b]				
5 mg/day	2155			
Rat, Day 168 (6-Month Study, Toxicology Report 4)				
60 mg/kg/day [c]	29100	82900	18	51
Dog, Day 176 (6-Month Study, Toxicology Report 23)				
10 mg/kg/day [d]	3772 to 6882	4105 to 6202	4-7	4-6
400 mg/kg/day [e]	31384 to 91270	41786 to 129341	32-92	42-130
Dog, Day 364 (12-Month Study, Toxicology Report 36)				
25 mg/kg/day [f, g]	8576 to 43136	8792 to 68012	9-43	9-68
Rat, Day 19 (Segment II/III, Toxicology Report 39, ADME Report 45)				
30 mg/kg/day [f]		55590		34

a Margin of Safety = (AUC in animals)*(fraction unbound)/(AUC in humans)*(fraction unbound). Multiple of unbound tadalafil calculated using in vitro protein binding. Mean percent bound in vitro in human plasma is 94%, in rat plasma is 92%, and in dog plasma is 87%.

b Plasma pharmacokinetic data used in calculations were determined at steady state following five daily doses of 5 mg tadalafil (market image) in healthy men and women (Study LVAU). In humans, no gender difference has been observed in pharmacokinetics parameters.

c No observed adverse effect level (NOAEL).

d No observed effect level (NOEL) for males.

e No observed adverse effect level (NOAEL) for females.

f No observed effect level (NOEL) for females.

g No observed effect level (NOEL) for males was not determined.

Ecotoxicity/environmental risk assessment

Taking into account the current usage due to the approved 10 and 20 mg tadalafil on demand dosing schedule and the predicted additional usage with the proposed 2.5 and 5 mg tadalafil once-a-day

dosing schedule, less than 3000 kg of the active ingredient in Cialis is expected to be used in a year in Europe resulting in maximum expected concentrations in the surface water of 0.003 µg/L.
Given its water solubility, low octanol-water partition coefficient, and low sludge-sorption coefficient, tadalafil is not expected to accumulate in sewage sludge or tissue.
Acute toxicity was not found for rainbow trout, daphnids or sewage-sludge microorganisms at the highest tested concentration, 2 mg/L (limited by water solubility).
The predicted no effect concentration (PNEC) is more than 650 times higher than the maximum concentration calculated for surface water.
Terrestrial mammals drinking sewage influent at a rate of 10% of their body weight per day would be exposed to tadalafil at a level that is more than 3 million times lower than the NOEL (10 mg/kg) determined in a 6- month dog toxicology study. The highest exposure from sewage influent would also be more than 16000 times lower than a therapeutic dose in humans.

Discussion on the non-clinical aspects

Having considered that doses up to 20 mg day of tadalafil are currently administered to patients and that non clinical findings have been evaluated in clinical studies and determined to be species specific with little relevance to clinical safety, the CHMP considered that the previously submitted non clinical program for 10 and 20 mg tadalafil could adequately support the new proposed doses of 2.5 and 5 mg tadalafil.

With respect to the safety margins, no further concerns were raised. Although continuous dosing may have a different pharmacological and toxicological profile than pulsatile dosing, the CHMP considered that this concern was adequately addressed with the previously submitted non clinical program for 10 and 20 mg tadalafil which included continuous administration.

With respect to the update of the environmental risk assessment, the CHMP concluded that the presented data suggested the environmental exposure to tadalafil to be expected very low, with concentrations far in excess of the NOEL observed in animal studies and therefore no concerns were anticipated.
However according to the ERA guideline (EMEA/CHMP/SWP/4447/00), the CHMP raised a concern about the lack of long-term toxicity data in fish. To address this issue, the MAH committed to conduct a standard early life stage study in fathed minnows (OECD Guideline 210) as a follow up measure, the study being initiated around Q3/2007.

4 Clinical aspects

Introduction

On 12 November 2002, the dose formulation originally authorised were tadalafil 10 mg and 20 mg film-coated tablets in the current approved indication i.e treatment of erectile dysfunction (ED).
The current approved dosage of 10 mg or 20 mg are intended for use prior to anticipated sexual activity and not recommended for continuous daily use.

The present extension application concerned new proposed doses of 2.5 and 5 mg tadalafil film-coated tablets to be used once a day in the treatment of erectile dysfunction. The proposed recommended starting dose is 5 mg tadalafil orally once a day for most patients. The 2.5 mg dose of tadalafil may provide efficacy for some men; therefore, the 5 mg tadalafil may be decreased to 2.5 mg tadalafil once a day based on individual tolerability.

The clinical development program to support these new proposed doses (5mg and 2.5 mg used once a day) consisted of the 3 phase III randomised, double-blind, placebo controlled, parallel design multicenter studies e.g:

- Study H6D-MC-LVCV (or LVCV) was to evaluate the efficacy and safety of tadalafil 5 mg and 10 mg once a day in male subjects with ED;

- Study H6D-MC-LVFP (or LVFP) was to evaluate the efficacy and safety of tadalafil 2.5 and 5 mg administered once a day in male subjects with ED;

- Study H6D-MC-LVFZ (or LVFZ) was to evaluate the efficacy and safety of tadalafil 2.5 mg and 5 mg administered once a day in male subject with diabetes mellitus and ED.

Previously, a number of studies to investigate the clinical pharmacology (e.g H6D-EW-LVBX , H6D-EW-LVAU) of tadalafil have been performed and submitted to support the current approved doses of 10 mg and 20 mg. The MAH referred to those studies to support the two proposed 2.5 and 5 mg strengths.

Additionally, to support the new dosing regimen 'once a day administration' for 2.5 and 5 mg tadalafil, the applicant provided a pharmacokinetic (PK) analysis from a subset of subjects enrolled in the Phase 3 study H6D-MC-LVFP. The results from this PK analysis were compared with the results obtained from a subset of subject enrolled in the Phase 3 study H6D-MC-LVCE 'as needed administration', previously submitted in the original MAA.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Pharmacokinetics for Once-a-Day Dosing of tadalafil 2.5 and 5 mg

The pharmacokinetic analysis included 359 concentration observations from 66 subjects administered tadalafil 2.5 or 5 mg once a day from Phase 3 study H6D-MC-LVFP. Data were analysed using population-based techniques.

The pharmacokinetic data obtained after once-a-day dosing of tadalafil 2.5 mg and 5 mg was described by a one-compartment model with a rapid first-order absorption rate (1.01 h-1).

The typical estimate (%SEE) for CL/F was 1.87 L/h (5.13%) and was similar to the value of approximately 1.6 L/h reported in Study H6D-MC-LVCE.

The final model predicted that a 70-kg individual would have a V/F of 50.8 L, which was consistent with tadalafil distribution into tissues.

Subject factors examined as potential covariates were prospectively defined based upon previous population pharmacokinetic analyses: dose group, age, body weight, BMI, height, GGT, investigator, time on therapy, history of cardiovascular disease, diabetes and ED severity. None of the covariates investigated were found to be a predictor of CL/F, and only body weight significantly influenced V/F.

- Comparative PK analysis between 'As-Needed Dosing' and 'Once-a-Day Dosing'

Typical CL/F estimates from studies LVCE and LVFP were similar. Furthermore, the 95% confidence intervals demonstrated considerable overlap, supporting the concordance across studies and dosing regimens.

The absorption, distribution, metabolism, and excretion of tadalafil were similar irrespective of as-needed or once-a-day administration.

Importantly, the similarity of ka, CL/F, and V/F values, and the distribution of these estimates between as-needed and once-a-day administration, indicated that systemic exposure to tadalafil was comparable between these regimens at equivalent doses and dosing intervals (See Table 2).

Table 2

Table 2.7.2.8. Comparison of Parameter Estimates (95% Confidence Interval) From Studies LVCE and LVFP

Protocol number	k_a (h^{-1})	CL/F (L/h)	V/F (L)
H6D-MC-LVCE[a]	1.86 (0.580 – 3.14)	1.99 (1.79 – 2.19)	63.8 (59.5 – 68.1)
H6D-MC-LVFP[b]	1.01 (0.758 – 1.34)	1.87 (1.70 – 2.08)	75.8 (65.8 – 88.3)

Abbreviations: CL/F = apparent clearance, k_a = absorption rate constant, V/F = apparent volume of distribution.

[a] The 95% confidence interval for each parameter was calculated by Parameter Estimate ± 1.96 SE.

[b] The 95% confidence interval for each parameter was obtained from parameter sensitivity analysis.

The systemic exposure to tadalafil was not influenced by cardiovascular conditions, diabetes, hepatic function (GGT), or severity of ED.

Clinical efficacy

- Main studies

Three Phase 3, randomized, double-blind, placebo-controlled, parallel-design, multicenter studies (LVCV, LVFP, and LVFZ) and two open-label extension periods (LVCV and LVFP) were conducted to support the proposed 2.5 and 5 mg new doses of tadalafil used as once a day dosing.

These studies were conducted in Australia (LVFZ), Europe (LVCV, LVFZ), Latin America (LVCV), Canada and Mexico (LVFZ) and US (LVFP, LVFZ). The design of these studies is summarised in Table 3.

Table 3

Table 2.7.3.1. Tadalafil Once-a-Day Dosing Phase 3 Placebo-Controlled Clinical Studies

Study	Centers	Population	Randomized Study Population	Design	Treatment Period	Treatment Groups	Coprimary Efficacy Endpoints
LVCV	20	ED	268	Double-blind placebo-controlled parallel group	12 weeks	Placebo Tadalafil 5 mg Tadalafil 10 mg	IIEF EF Domain SEP Q2 SEP Q3
LVFP	15	ED	287	Double-blind placebo-controlled parallel group	24 weeks	Placebo Tadalafil 2.5 mg Tadalafil 5 mg	IIEF EF Domain SEP Q2 SEP Q3
LVFZ	23	ED and diabetes	298	Double-blind placebo-controlled parallel group	12 weeks	Placebo Tadalafil 2.5 mg Tadalafil 5 mg	IIEF EF Domain SEP Q2 SEP Q3

Abbreviations: ED = erectile dysfunction, EF = erectile function, IIEF = International Index of Erectile Function, SEP = Sexual Encounter Profile.

METHODS

Efficacy endpoints

Each study used the same three co-primary efficacy variables: the Erectile Function (EF) Domain of the International Index of Erectile Function (IIEF) and patient Sexual Encounter Profile diary (SEP) Questions 2 (Q2) and 3 (Q3).

Secondary measures included the IIEF Intercourse Satisfaction Domain, the Overall Satisfaction Domain, individual IIEF questions 3 and 4, SEP Q4 and Q5 and the partner SEP diary, the two Global Assessment Questions (GAQ).

Additional secondary endpoints were: Psychological and Interpersonal Relationship Scales (PAIRS) in study LVFP; the proportion of subjects with an IIEF EF Domain score <26 at baseline that achieved an IIEF EF Domain score ≥26 at endpoint (indicating "no ED"), Self-Esteem and Relationship Questionnaire (SEAR) and Rosenberg Self-Esteem Scale (RSE) in study LVFZ.

Study design

Study periods were as follows: 4-week treatment-free run-in period (studies LVCV, LVFP, LVFZ) + Placebo-controlled double-blind treatment period (12 weeks in studies LVCV and LVFZ; 24 weeks in study LVFP) + one-year (study LVCV) or 2-year (study LVFP) open-label extension period of tadalafil 5 mg once-a-day dosing + four-week treatment-free follow-up period (study LVCV).

Only the planned 1-year interim analysis of Study LVFP is included in this present application since the second year open-label extension period is ongoing.

Statistical method

Primary and secondary outcomes were analysed on an intent-to-treat basis, using the last-observation-carried-forward (LOCF) methods. IIEF responses were analysed as change from baseline to study endpoint. The endpoint SEP score was the subject's percentage of 'yes' responses to that question at the end of the treatment period or final treatment visit.

Efficacy for the extension period has been evaluated by comparing IIEF EF Domain baseline values prior to the placebo-controlled period with the extension period endpoint values.

Significance for the co-primary efficacy endpoints was declared if and only if the p-values for the individual hypotheses tests were all <0.05. No adjustments for testing multiple endpoints were applied to the primary efficacy analyses.

Study populations

Studies LVCV and LVFP

- inclusion criteria: subjects (≥18 years old) with at least a 3-month history of mild to severe ED of psychogenic, organic, or mixed etiology. ED was defined as a consistent change in the quality of erection that adversely affected satisfaction with sexual intercourse.

- main exclusion criteria: ED secondary to other primary sexual disorders or endocrinopathy, radical prostatectomy (with the exception of bilateral nerve-sparing prostatectomy), ineffective prior treatment with sildenafil citrate in the opinion of the investigator (study LVCV), ineffective treatment with phosphodiesterase type 5 (PDE5) inhibitors (study LVFP).

- study treatment arms: Tadalafil 2.5 mg once a day (study LVFP), Tadalafil 5 mg once a day (studies LVCV and LVFP), Tadalafil 10 mg once a day (study LVCV). Placebo treatment groups were included in both studies.

- randomisation: subjects were stratified by geographic region and baseline IIEF EF Domain score categories: mild (17 through 30), moderate (11 through 16), and severe (1 through 10). Subjects were then randomly assigned to treatment groups in a 1:2:2 manner (placebo, tadalafil 5 mg, and tadalafil 10 mg) for study LVCV, and a 1:1:1 manner (placebo, tadalafil 2.5 mg, tadalafil 5 mg) for study LVFP.

Study LVFZ

Eligibility (Inclusion/Exclusion) criteria for study LVFZ were similar to studies LVCV and LVFP. However, all subjects in Study LVFZ also had at least a 3-month history of diabetes.
Patients were randomised to tadalafil 2.5 mg once a day, tadalafil 5 mg once a day, or placebo (1.1:1).

RESULTS

Demographic and baseline characteristics

The demographics and baseline characteristics of the study populations in studies LVCV, LVFP, and LVFZ were similar except all subjects in study LVFZ had diabetes mellitus.

Overall, the proportion of patients older than 65 years ranged from 23% to 29% across studies, with a slightly higher proportion of patients older than 65 years old in study LVFP. Patients were well balanced across treatment groups and across studies with regard to erectile dysfunction severity.

The predominant ethnic origin in tadalafil once-a-day dosing studies was Caucasian (>82%).

Approximately 14% to 15% of subjects in the general population studies had diabetes. All subjects in study LVFZ had diabetes. The percentage of subjects with systemic arterial hypertension was also lower in study LVCV (ranging between 25.7% and 34.3% across treatment groups) while in studies LVFP and LVFZ ranged from 40.6% to 55.0%). Fewer subjects in study LVCV (from 32.1% to 43%) reported a history of cardiovascular disease at baseline than those in studies LVFP (47% to 53.2%) and LVFZ (60.0% to 63.3%).

Demographics and baseline characteristics were generally similar for general population studies in the once-a-day dosing and the as-needed dosing programs, with a lower proportion of diabetic patients in the once-a-day studies and a higher proportion of subjects who had hypertension and cardiovascular diseases.

For stratification and data analysis, ED severity was categorised based on the baseline IIEF EF Domain score as mild (score of 17-30), moderate (score of 11-16), or severe (score of 1-10). Mean IIEF EF Domain scores at baseline of each treatment group ranged from 12.6 to 14.1 (moderate ED severity category).

Subjects were included based on a clinical diagnosis of ED. Forty-nine subjects who had a baseline IIEF EF Domain score of 26 or greater ("no ED") were included.

Studies LVCV and LVFP (including open label extension periods)

Recruitment / Numbers analysed

- *Study LVCV* included 268 subjects (54 subjects in the placebo group and 214 subjects in the tadalafil treatment groups) with an average age of 56 years. A total of 234 subjects (87.3%) completed the placebo-controlled double-blind treatment period. Most of the subjects that completed the treatment period enrolled in the open-label extension period (n=183, 78%). A protocol addendum allowed 51 additional and new subjects from Argentina to enroll directly into the open-label extension period to meet the enrolment requirements. Thus, a total of 234 subjects were enrolled and 208 subjects completed the open-label extension period. A total of 207 subjects completed the treatment-free follow-up period.

- *Study LVFP* included 287 subjects (94 subjects in the placebo group and 193 subjects in the tadalafil treatment groups) with an average age of 60 years. Most of the subjects (N=238, 82.9%) completed the placebo-controlled double-blind treatment period. A total of 238 subjects enrolled in the tadalafil 5 mg 2-year open-label extension period. A total of 162, (68.1%) completed the first year of the 2-year open-label extension period.

Efficacy – Co-primary Endpoints

Results are shown for studies LVCV and LVFP in Tables 4 and 5

Table 4

Table 2.7.3.3. Coprimary Endpoint Results Placebo-Controlled Double-Blind Period Once-a-Day Study LVCV

	Placebo Mean ± SD	Tadalafil 5 mg Mean ± SD	Tadalafil 10 mg Mean ± SD
IIEF EF Domain	(n=54)	(n=107)	(n=105)
Baseline	14.1 ± 7.3	13.0 ± 5.9	13.4 ± 6.2
Endpoint	15.0 ± 8.4	22.8 ± 7.7	22.8 ± 8.1
Change	0.9 ± 5.7	9.7* ± 8.7	9.4* ± 8.2
SEP Question 2 (% yes)	(n=52)	(n=105)	(n=103)
Baseline	40.5 ± 40.9	43.0 ± 39.9	41.8 ± 38.0
Endpoint	51.7 ± 40.8	79.4 ± 30.5	81.2 ± 33.2
Change	11.2 ± 30.7	36.5* ± 41.5	39.4* ± 36.8
SEP Question 3 (% yes)	(n=51)	(n=105)	(n=103)
Baseline	23.5 ± 32.9	21.8 ± 31.1	22.7 ± 31.8
Endpoint	36.7 ± 38.3	67.2 ± 38.2	72.8 ± 35.9
Change	13.2 ± 26.4	45.5* ± 43.9	50.1* ± 37.1

Abbreviations: ANCOVA = analysis of covariance, EF = erectile function, IIEF = International Index of Erectile Function, SD = standard deviation, SEP = patient Sexual Encounter Profile diary.
* p<.001 versus placebo by ANCOVA, adjusted for multiple comparison by the method of Dunnett.
Source: RMP.H6DO.LVCV (EF272001, EF275001, EF276001).

Table 5

Table 2.7.3.4. Coprimary Endpoint Results at 12 Weeks Placebo-Controlled Double-Blind Period Once-a-Day Study LVFP

	Placebo Mean ± SD	Tadalafil 2.5 mg Mean ± SD	Tadalafil 5 mg Mean ± SD
IIEF EF Domain	(n=93)	(n=93)	(n=96)
Baseline	13.4 ± 6.1	13.0 ± 6.5	13.7 ± 6.1
Endpoint	14.9 ± 8.3	19.2 ± 9.1	21.0 ± 8.3
Change	1.5 ± 5.9	6.2* ± 7.9	7.2* ± 7.2
SEP Q2 (% yes)	(n=92)	(n=92)	(n=96)
Baseline	45.9 ± 37.1	41.0 ± 35.6	44.5 ± 36.2
Endpoint	49.7 ± 37.8	64.9 ± 37.7	70.9 ± 35.2
Change	3.8 ± 25.8	23.9* ± 31.8	26.4* ± 32.2
SEP Q3 (% yes)	(n=92)	(n=92)	(n=96)
Baseline	21.8 ± 28.6	18.8 ± 26.5	21.8 ± 30.7
Endpoint	30.7 ± 34.1	50.2 ± 38.5	57.1 ± 36.7
Change	8.9 ± 24.6	31.3* ± 34.1	35.3* ± 33.1

Abbreviations: ANCOVA = analysis of covariance, EF = erectile function, IIEF = International Index of Erectile Function, Q = question, SD = standard deviation, SEP = patient Sexual Encounter Profile diary.
* p<.001 versus placebo by ANCOVA, adjusted for multiple comparison by the method of Dunnett.
Source: RMP.H6DO.LVFP (EFH01FPD, EFH01FPE, EFH01FPF).

Tadalafil 2.5 mg, 5 mg and 10 mg once-a-day dosing significantly improved erectile function compared with placebo for each of the co-primary endpoints at 12 weeks ($p<0.001$ each tadalafil group).

Efficacy – Secondary Endpoints

- GAQ Q1 and GAQ Q2

The proportions of subjects with positive responses to *GAQ Q1* at the end of the 12-week treatment periods were as follows: 29.6%, placebo (study LVCV); 28.6%, placebo (study LVFP); 66.0%, tadalafil 2.5 mg; 84.5%, tadalafil 5 mg (study LVCV); 76.1%, tadalafil 5 mg (study LVFP); 84.6%, tadalafil 10 mg.

The proportions of subjects with positive responses to *GAQ Q2* were as follows: 27.8%%, placebo (study LVCV); 24.2%, placebo (study LVFP), 60.6%, tadalafil 2.5 mg; 77.7%, tadalafil 5 mg (study LVCV); 72.8%, tadalafil 5 mg (study LVFP); 80.8%, tadalafil 10 mg.

- *IIEF Intercourse Satisfaction and IIEF Overall Satisfaction Domain* scores

IIEF Intercourse Satisfaction and IIEF Overall Satisfaction Domain scores were similar among all of the treatment groups and scores improved significantly with tadalafil 2.5 mg, 5 mg, and 10 mg once-a-day dosing compared with placebo.

IIEF Intercourse Satisfaction Domain score placebo-adjusted mean changes from baseline (LS mean differences) were as follows: 1.1, tadalafil 2.5 mg; 3.1, tadalafil 5 mg (study LVCV); 1.9, tadalafil 5 mg (study LVFP); 2.7, tadalafil 10 mg.

IIEF Overall Satisfaction Domain score placebo-adjusted mean changes from baseline (LS mean differences) were as follows: 1.0, tadalafil 2.5 mg; 2.0, tadalafil 5 mg (study LVCV); 1.6, tadalafil 5 mg (study LVFP); 2.3, tadalafil 10 mg.

The proportion of subjects who achieved an IIEF EF Domain score ≥26 was higher for all tadalafil groups compared with placebo: placebo 8.3% (study LCVC) and 14.1% (study LVFP), tadalafil 2.5mg 37.8%, tadalafil 5mg 51.5% (study LCVC) and 42.4% (study LVFP), Tadalafil 10mg 50.5%.

- *Patient Sexual Encounter Profile Diary: SEP Q3: "Did your erection last long enough for you to have successful intercourse?"*

The overall percentages of successful intercourse attempts were higher for all tadalafil groups compared with placebo: 38.8%, placebo (study LVCV); 33.5%, placebo (study LVFP); 53.0%, tadalafil 2.5 mg; 68.6%, tadalafil 5 mg (study LVCV); 62.3%, tadalafil 5 mg (study LVFP); 78.5%, tadalafil 10 mg.

- *SEP Q4: "Were you satisfied with the hardness of your erection?"and SEP Q5: "Were you satisfied overall with this sexual experience?"*

The percentage of 'yes' responses to SEP Q4 and SEP Q5 at baseline was generally similar among studies and treatment groups.

For SEP Q4: 21.3%, tadalafil 2.5 mg; 34.7%, tadalafil 5 mg (study LVCV); 25.3%, tadalafil 5 mg (study LVFP); 40.2%, tadalafil 10 mg.

For SEP Q5: 20.8%, tadalafil 2.5 mg; 35.7%, tadalafil 5 mg (study LVCV); 24.1%, tadalafil 5 mg (study LVFP); 41.7%, tadalafil 10 mg.

Study LVFZ

Recruitment / Numbers analysed

The randomised study population included 298 subjects with an average age of 57 years. Most of these subjects (N=254, 85.2%) completed the placebo-controlled double-blind treatment period.

Efficacy – Co-primary Endpoints

Results of the co-primary endpoints are summarised in Table 6.

Table 6

Table 2.7.3.5. Coprimary Endpoint Results Placebo-Controlled Double-Blind Period Once-a-Day Study LVFZ

	Placebo Mean ± SD	Tadalafil 2.5 mg Mean ± SD	Tadalafil 5 mg Mean ± SD
IIEF EF Domain	(n=98)	(n=97)	(n=97)
Baseline	13.4 ± 6.6	13.5 ± 6.5	12.7 ± 6.2
Endpoint	14.7 ± 8.8	18.3 ± 8.7	17.2 ± 8.9
Change	1.3 ± 6.2	4.8* ± 7.5	4.5** ± 7.2
SEP Q2 (% yes)	(n=95)	(n=96)	(n=95)
Baseline	37.7 ± 40.1	41.8 ± 40.8	32.2 ± 38.1
Endpoint	43.0 ± 42.0	62.3 ± 41.7	61.1 ± 39.8
Change	5.3 ± 24.3	20.5* ± 33.3	28.9* ± 36.3
SEP Q3 (% yes)	(n=95)	(n=96)	(n=95)
Baseline	20.1 ± 30.1	20.1 ± 31.0	16.1 ± 28.8
Endpoint	28.2 ± 34.7	46.0 ± 40.6	41.1 ± 39.0
Change	8.2 ± 24.9	25.9* ± 36.3	25.0* ± 31.2

Abbreviations: ANCOVA = analysis of covariance, EF = erectile function, IIEF = International Index of Erectile Function, Q = question, SD = standard deviation, SEP = patient Sexual Encounter Profile diary.
* p<.001 versus placebo by ANCOVA, adjusted for multiple comparison by the method of Dunnett.
**p=.005 versus placebo by ANCOVA, adjusted for multiple comparison by the method of Dunnett.
Source: RMP.H6DO.LVFZ (EFZ01FZA, EFZ01FZB, EFZ01FZC).

Tadalafil 2.5 mg and 5 mg once-a-day dosing significantly improved erectile function compared with placebo for each of the coprimary endpoints at 12 weeks.

Open-Label Extension Periods (studies LVCV and LVFP)

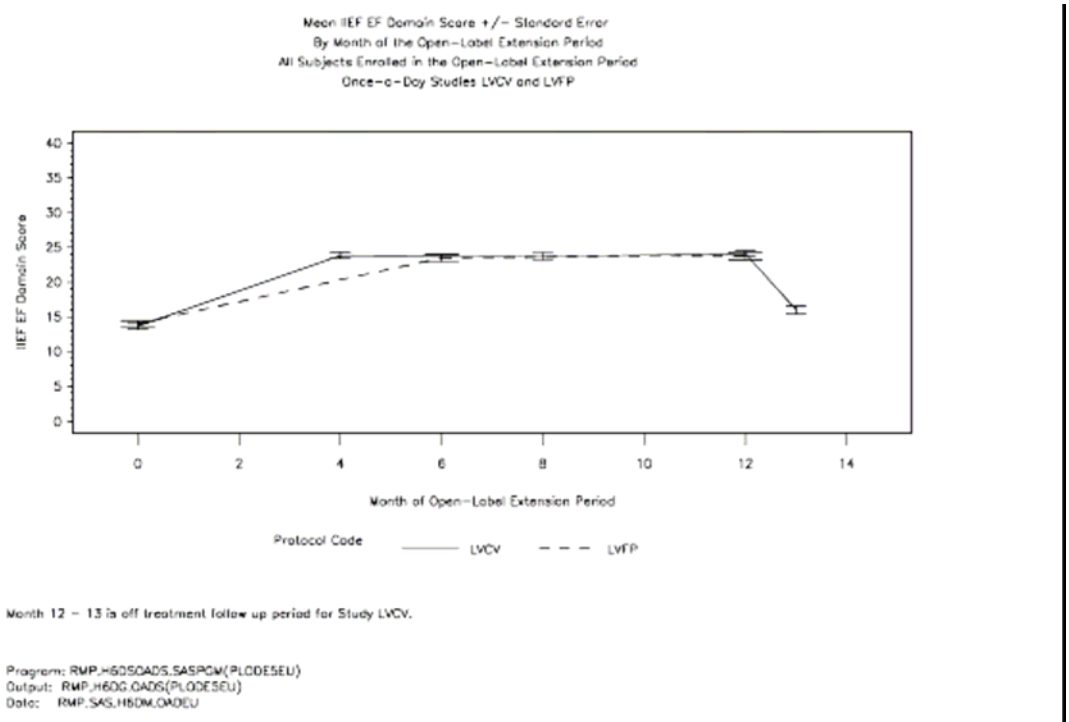
The open-label periods of Studies LVCV and LVFP enrolled 472 subjects (N=234, LVCV; N=238, LVFP). Most subjects continued from the placebo-controlled double-blind treatment periods. Some subjects directly entered the extension period of Study LVCV (n=51). Most subjects (88.5%, LVCV; 68.1%, LVFP) completed the extension periods. Discontinuation due to perceived lack of efficacy was lower for Study LVCV (3.4%) than for Study LVFP (14.7%).

The mean IIEF EF Domain score was 13.7 at baseline and 23.3 at the end of the extension period for all subjects enrolled in the extension period of Study LVCV.

In Study LVFP, the mean IIEF EF Domain score was 14.0 at baseline of the placebo-controlled period and 22.8 at endpoint of the extension period for all subjects enrolled in the extension period.

In Study LVCV, the mean IIEF EF Domain score decreased markedly from 24.1 at the end of the extension period to 16.0 after the 4-week treatment-free follow-up period. This assessment included subjects (n=206) that had IIEF EF Domain scores for both endpoint and the post-treatment-free follow-up period visits (see figure 1).

Figure 1



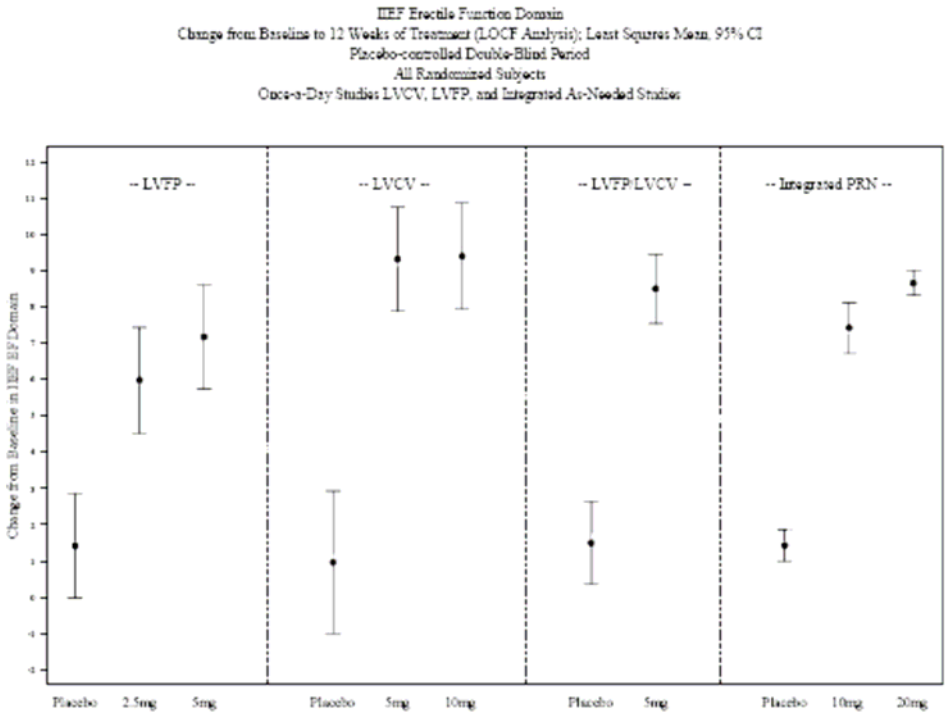
ure 2.7.3.4. Mean IIEF EF Domain scores over 1 year of tadalafil 5 mg once-a-day dosing: open-label extension periods of Studies LVCV and LVFP.

Dose selection

The efficacy of tadalafil 5 mg once-a-day dosing was greater than the efficacy achieved with 2.5 mg once-a-day dosing and demonstrated equivalent efficacy to that of tadalafil 10 mg as-needed dosing.

Integrated efficacy data from the placebo-controlled studies in the general ED population showed that tadalafil 5 mg once-a-day dosing results in higher IIEF EF Domain scores and higher proportions of 'yes' responses to SEP Q2 than those observed for tadalafil 10 mg as-needed dosing with some overlap in the 95% confidence intervals between the doses (see figure 2).

Figure 2



3.1. Comparison of IIEF EF Domain score mean changes from baseline by study, tadalafil as-needed versus once-a-day dosing.

The proportions of 'yes' responses to SEP Q3 were similar for tadalafil 5 mg once-a-day dosing and tadalafil 10 mg as-needed dosing with substantial overlap in the 95% confidence intervals.

Fewer subjects receiving tadalafil 5 mg once-a-day dosing experienced adverse events known to be associated with tadalafil administration compared with subjects receiving tadalafil 10 mg as-needed dosing, and the incidence of adverse events was similar for both the tadalafil 5 mg and 2.5 mg doses.

In view of these data, tadalafil 5 mg once-a-day dosing was selected by the MAH as an alternative regimen to tadalafil 10 mg as-needed dosing in the general ED population. Although lower efficacy has been observed for tadalafil 2.5 mg once-a-day dosing, the MAH proposed to use this dose for male patients who do not tolerate tadalafil 5 mg once-a-day dosing.

- Clinical study in special population

In study LVFZ conducted in the diabetic population, tadalafil 2.5 mg and 5 mg once-a-day dosing significantly improved erectile function compared with placebo for each of the coprimary endpoints at 12 weeks.
In the integrated analysis (including patients with diabetes mellitus from studies LVCV, and LVFP), response rates for SEP Q2 and SEP Q3 were 15.4-20.9% and 15-17.6%, respectively.

- Other supportive data

Vernet et al. examined PDE5 expression and cGMP concentrations during 14 days of continuous incubation of human penile corpora cavernosal smooth muscle cells and fibroblasts of the tunica albuginea with tadalafil at concentrations well above the IC50 (concentration of tadalafil inhibiting 50% of PDE5 activity in vitro) and around the Cmax (mean peak plasma concentration in vivo).

No up-regulation of PDE5 expression or decrease in cGMP concentrations was observed, suggesting that tachyphylaxis, particularly via transcriptional activation, is not likely to occur with clinical use.

- Discussion on Pharmacokinetics and Clinical Efficacy

Pharmacokinetics

A review of the pharmacokinetics of tadalafil at doses of 2.5mg to 20mg following single and multiple doses showed that the average Cmax achieved following single doses of tadalafil 10 and 20mg are approximately 1.3-fold and 2.6-fold, respectively, of those achieved following once-a-day administration of tadalafil 5 mg at steady-state.

Similarly, the daily systemic exposure (AUC-24h) following single doses of tadalafil 10 and 20mg were approximately 1.2-fold and 2.4-fold, respectively, of those expected at steady-state following once-a-day administration of tadalafil 5mg. Based on these data, repeated once-a-day administration of tadalafil 2-5 and 5mg did not result in higher Cmax and total systemic exposure than that following single administration of 10 or 20 mg tadalafil doses.

Pharmacokinetic sample analysis from studies LVFP and LVCE showed that systemic exposure to tadalafil was comparable for the 'once a day' and 'as needed' dosing regimens.

With respect to PK/PD interactions, the MAH referred to the previously submitted studies supportive of the initial MA for 10mg and 20mg tadalafil as-needed dosing. These studies demonstrated the lack of clinically relevant PK interactions. However, the CHMP considered that direct extrapolation of these results, could be questionable since most of the studies were performed following the current clinical practice use i.e patients on a stable regimen with any concomitant therapy (monotherapy) received a single dose of tadalafil.

In view of the above CHMP's concern, the MAH provided a detailed analysis of the available PK/PD data which were in overall reassuring. As requested by regulatory authorities, Two interaction studies with alpha-blockers (tamsulosin and doxazosin) following once-a-day doses of tadalafil 5 mg are ongoing at the time of the present application. Preliminary data showed relevant PD interaction with doxazosin. This concern has been addressed in the Product Information.

Clinical Efficacy

The design of the three phase III studies was similar to that of the pivotal studies performed to support the MAA of tadalafil as-needed dosing.

Results from studies LVCV and LVFP showed a statistically significant improvement for each of the co-primary endpoints in patients treated with all doses of tadalafil (2.5mg, 5mg, 10mg) compared to placebo.

No differences between tadalafil 5mg and 10mg once-a-day dosing were observed, while differences between 2.5mg and 5mg were numerical.

Differences in the magnitude of the response across the studies were observed. In study LVFP, tadalafil 5mg once-a-day showed similar results to tadalafil 10 mg as-needed dosing, which was expected since similar drug exposure was observed between the 2 dosages. In study LVCV, the efficacy of tadalafil 5 mg once-a-day in Study LVCV was, unexpectedly, similar to that of tadalafil 20 mg as-needed dosing.

Results from study LVFZ showed statistically significant differences for each of the primary endpoints between tadalafil and placebo groups, thus confirming a marginal benefit of tadalafil chronically used in patients with diabetes mellitus. In this special population, the magnitude of change for each of the co-primary endpoints was lower as compared to the 'as-needed' regimen. Furthermore, analyses of the proportion of successful intercourses (SEP question 3) showed that less than half of the attempts were successful (i.e. 41-46%).

The CHMP was also concerned about the lack of a direct comparison of the efficacy profile between both regimens ie. once-a-day versus as-needed administrations.
The MAH estimated the relative efficacy of tadalafil once a day dosing versus the currently authorised dosing regimen by comparing efficacy results across different studies, although the limitations of such analysis were known.

In view of the above CHMP's concerns, an efficacy analysis by means of the proportion of successful intercourses across treatment groups was performed to allow an objective assessment of the magnitude of the clinical benefit. The proportion of responders i.e, patients who achieved normal ED with treatment (score ≥ 26) to previous treatment of other PDE5 inhibitors across studies LVCV and LVFP was also analysed.

Results showed that the clinical benefit of tadalafil as 'once a day' dosing was less than double of the placebo, which could be considered the minimum acceptable effect to support the chronic use.

Minor differences in the proportion of responders to previous treatment among tadalafil 5mg treatment groups in studies LVCV and LVFP were observed. Although efficacy results appeared similar between both populations (naive and responders to PDE5 inhibitors treatment), a vast majority of patients included in these studies were responders to previous PDE5 inhibitors.

Analysis of responders was also considered by CHMP to address the issue on the clinical relevance of the effect of tadalafil once a day dosing. Across all studies and severities, 42-52% of patients who received 5mg of tadalafil once a day improved to the no-ED category at endpoint, compared with 28% for the 2.5mg tadalafil patient group and 8-14% for the placebo patient group. Similar response rates were observed as compared to'as needed' dosing.

Overall, the CHMP was of the opinion that the clinical data supported some evidence that the once-a-day regimen might be a suitable alternative for the subset of patients with ED with frequent sexual intercourse attempts (e.g. at least twice weekly) for a limited period and according to the treating physician judgement and patient convenience.
Nevertheless, the CHMP considered that the new proposed dosage regimen would only apply to this restricted population, as the once-a-day treatment could represent excessive dosing for men with ED and who have infrequent need for medication to facilitate sexual activity.

With respect to the dose selection, the use of tadalafil 5 mg for the recommended once-a-day dosing in the general ED population, was considered acceptable by CHMP. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

Clinical safety

- Patient exposure

The 3 placebo-controlled once-a-day dosing studies included a total of 853 subjects (N=268, LVCV; N=287, LVFP; N=298, LVFZ). A total of 472 subjects (N=234, LVCV; N=238, LVFP) enrolled in the extension periods. Most subjects (85.1%) completed the double-blind treatment period. Most subjects (78.2%) completed the 1-year open-label extension periods (88.5%, LVCV; 68.1%, LVFP first year).

A total of 617 subjects have had at least 6 months of exposure to tadalafil 5 mg, 10 mg, or 20 mg once-a-day dosing and 388 subjects have had at least 1 year of exposure to tadalafil 5 mg once-a-day dosing.

- Adverse events

The incidence of treatment-emergent adverse events in the 12-week, placebo-controlled once-a-day integrated data was generally higher for tadalafil-treated subjects compared with placebo. The highest incidence of treatment-emergent adverse events was observed in the tadalafil 10 mg once-a-day dosing group (57.1%). The incidence of treatment-emergent adverse events was similar between the tadalafil

5 mg and 2.5 mg once-a-day dosing groups (5 mg, 47.4%; 2.5 mg, 50.0%), and lower for the placebo group (36.3%). The incidence of serious adverse events, however, was similar between tadalafil- and placebo-treated subjects.

The incidence of treatment-emergent adverse events in the 19-study integrated database for tadalafil as-needed dosing (10 mg, 46.2%; 20 mg, 47.5%) was similar to the incidence of treatment-emergent adverse events observed for tadalafil 5 mg and 2.5 mg once-a-day dosing.

In the 1-year, long-term, open-label extension periods, when all subjects received tadalafil 5 mg once-a-day dosing, the overall incidence of treatment-emergent adverse events was 57.2%. This incidence was lower than the incidence of treatment-emergent adverse events during the first year of the open-label, tadalafil as-needed comparator study (65.3%).

In the 12-week, placebo-controlled integrated data, common treatment-emergent adverse events in the tadalafil 5 mg once-a-day dosing group were headache (5.6%), dyspepsia (4.6%), nasopharyngitis (3.3%), back pain (3.0%), upper respiratory tract infection (2.6%), flushing (2.6%), influenza (2.3%), and myalgia (2.3%). The summary of the treatment emergent adverse events is shown in Table 7.

Table 7

Table APP.2.7.4.4. Summary of Treatment-Emergent Adverse Events
By Decreasing Frequency of Occurrence in Subjects Receiving 5 mg Tadalafil Daily
Placebo-Controlled Double-Blind Period
All Randomized Subjects
Integrated Placebo-Controlled Once-a-Day Studies

	Integrated Placebo-controlled Once-a-Day Studies (a)			
	Treatment Groups			
Prefered Term	Placebo (N=248) n %	IC_2.5mg (N=196) n %	IC_5mg (N=304) n %	IC_2.5/5mg (N=500) n %
PATIENTS WITH >=1 TEAE	90 (36.3)	98 (50.0)	144 (47.4)	242 (48.4)
PATIENTS WITH NO TEAE	158 (63.7)	98 (50.0)	160 (52.6)	258 (51.6)
Headache	13 (5.2)	5 (2.6)	17 (5.6)	22 (4.4)
Dyspepsia	4 (1.6)	6 (3.1)	14 (4.6)	20 (4.0)
Nasopharyngitis	9 (3.6)	8 (4.1)	10 (3.3)	18 (3.6)
Back pain	3 (1.2)	6 (3.1)	9 (3.0)	15 (3.0)
Flushing	2 (0.8)	2 (1.0)	8 (2.6)	10 (2.0)
Upper respiratory tract infection	3 (1.2)	6 (3.1)	8 (2.6)	14 (2.8)
Myalgia	3 (1.2)	4 (2.0)	7 (2.3)	11 (2.2)
Influenza	5 (2.0)	6 (3.1)	7 (2.3)	13 (2.6)
Pain in extremity	0 (0.0)	1 (0.5)	5 (1.6)	6 (1.2)
Diarrhoea	1 (0.4)	2 (1.0)	5 (1.6)	7 (1.4)
Nasal congestion	0 (0.0)	4 (2.0)	5 (1.6)	9 (1.8)
Cough	1 (0.4)	7 (3.6)	5 (1.6)	12 (2.4)
Gastritis	0 (0.0)	0 (0.0)	4 (1.3)	4 (0.8)
Arthralgia	0 (0.0)	1 (0.5)	4 (1.3)	5 (1.0)
Paraesthesia	0 (0.0)	0 (0.0)	3 (1.0)	3 (0.6)
Sinus congestion	0 (0.0)	0 (0.0)	3 (1.0)	3 (0.6)
Abdominal pain upper	0 (0.0)	1 (0.5)	3 (1.0)	4 (0.8)

Note: Same subject may be counted in more than one category.
(a) Once-a-Day studies include LVCV, LVFP (12-week), LVPZ.
IC_2.5/5 = subjects assigned to either 2.5mg tadalafil or 5mg tadalafil
MEDDRA VERSION: 8.0

Generally, lower incidences of common treatment-emergent adverse events in the tadalafil 10 mg group were observed as compared to the 'as-needed' dosing placebo-controlled studies (headache, 10.2%; dyspepsia, 5.5%; nasopharyngitis, 5.2%; back pain, 3.8%; upper respiratory tract infection [0.5%;exception, lower than tadalafil 5 mg once-a-day dosing] flushing, 2.7%; influenza, 2.8%; and myalgia, 3.0%).

In the tadalafil 2.5 mg once-a-day dosing group, incidences of common treatment-emergent adverse events were similar or higher to those observed in the tadalafil 5 mg once-a-day group, except for headache (2.6%), dyspepsia (3.1%), and flushing (1.0%).

In the 1-year, open-label extension periods, common treatment-emergent adverse events were dyspepsia, 6.4%; headache, 5.5%; back pain, 5.5%; hypertension, 3.6%; influenza, 3.4%; nasopharyngitis, 3.0%; bronchitis, 2.1%; and sinusitis, 2.1% , with headache, dyspepsia, back pain, influenza and nasopharyngitis.

Sinusitis was the only common treatment-emergent adverse event that occurred in once-a-day dosing at an incidence ≥1% higher than the incidence at which it occurred in the as-needed comparator study.

The incidence of adverse events considered possibly related to study medication by the investigator in the 12-week, placebo-controlled once-a-day integrated data generally increased with increasing tadalafil dose (2.5 mg, 10.7%; 5 mg, 19.7%; 10 mg, 35.2%; placebo, 5.6%).

The most common possibly related adverse events in the integrated tadalafil 5 mg once-a-day dosing group, by preferred term, were headache (5.6%), dyspepsia (3.0%), flushing (2.6%), and back pain (2.0%).

In the tadalafil 2.5 mg once-a-day dosing group, incidences of possibly related adverse events for the same preferred terms were lower than tadalafil 5 mg once-a-day dosing and tadalafil 10 mg as-needed dosing (headache, 2.0%; dyspepsia, 2.6%; flushing, 0.5%; back pain, 1.5%).

- Deaths and other serious adverse events

There were 3 reports of death in patients who received 5 mg tadalafil once-a day dosing: one in the placebo-controlled period of study LVCV, 2 in the long-term extension period of Study LVFP. These were not considered related to study treatment.

Overall, the proportion of patients experiencing SAEs in the 12-week placebo-controlled once-a-day studies was 2.0 % in placebo, 1.5% in tadalafil 2.5mg, and 1.6% in tadalafil 5mg groups as compared to 1%, 0.7% and 1.2% in placebo, tadalafil 10mg and tadalafil 20mg 'as-needed' dosing.

In the 1-year, open-label extension periods, when all subjects received tadalafil 5 mg once-a-day dosing, 13 subjects in LVCV (9 tadalafil and 4 placebo) and 18 subjects in LVFP (12 tadalafil and 6 placebo) experienced a SAE. 'Fall' occurred in more than 1 subject as a SAE i.e 2 tadalafil and two placebo subjects. None of the reported 'falls' were considered related to study medication by the investigator.

- Other safety findings

The numbers of subjects who experienced decreases in systolic blood pressure (SBP) of at least 20 mm Hg ranged from 16.7% to 22%, with no differences among treatment groups. Only 2 cases were related to hypotensive events.

In placebo-controlled studies LVFP and LVCV, higher incidence of 'abnormal rhythms' in tadalafil 2.5 mg (20.6%) and 5 mg (23.1%) once-a-day dosing groups than in placebo (10.9%) was observed.

In subjects receiving tadalafil 2.5 mg and 5 mg once-a-day dosing, a higher incidence of dizziness was observed in subjects older than 65 years of age compared with younger subjects (> 65 years, 2.3%; ≤ 65 years, 0.5%).

- Discontinuation due to adverse events

During the placebo-controlled treatment periods, few subjects (n=32, 3.8%) discontinued study participation early due to an adverse event (2.8% in placebo vs 3-5.7% in tadalafil groups). Similarly, during the extension periods, few subjects (n=18, 3.8%) discontinued study participation early due to an adverse event.

- Discussion on clinical safety

The reported exposure to tadalafil at a once-a-day dosing regimen was in accordance with the ICH E1 guideline on *'the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions'* (CPMP/ICH/375/95).

The proportion of patients that completed the 12-weeks double blind period was similar across treatment groups and studies (ranging from 84% to 87%). Of these, 2.8% of patients discontinued due to AEs in placebo as compared to 3.0-5.7% in tadalafil treatment groups. Lack of efficacy was the reason for discontinuation in 8.9% of patients in placebo vs 1.5-3.0% in tadalafil groups during the double blind 12-week treatment period.

Of the 472 patients enrolled in the extension studies, 88.5% completed the 1-year open-label extension period in Study LVCV while up to 32% of patients in Study LVFP discontinued. During the first year, One third of patients discontinued therapy. Of these, up to 15% of patients perceived lack of efficacy as the reason for discontinuation.

The overall incidence of treatment emergent AEs in the double-blind once a-day studies was 47.4%, 50% and 57.1% in tadalafil 2.5mg, 5mg and 10mg treatment groups, respectively, as compared to 36.3% in placebo groups. Similar incidences were observed in the as-needed dosing studies.

The most common reported AEs were headache, dyspesia, back pain, flushing, myalgia, nasal congestion and pain in extremity. Incidence of these common AEs was lower than the one observed in the as-needed dosing studies.

Nevertheless, the proportion of serious AEs was slightly higher in the once-a-day dosing studies (SAE: 1.5-1.6% in tadalafil 2.5 and 5mg once-a-day versus 0.7% in tadalafil 10 mg as-needed dosing) as well as the rate of discontinuation due to AEs (2.6-4.1% in tadalafil 5mg and 2.5mg versus 1.3% in tadalafil 10mg as-needed dosing).

By contrast, in the open-label extension periods, a lower incidence of treatment emergent AEs, treatment related AEs, and rate of discontinuation in the tadalafil 5mg once-a-day treatment was observed as compared to the pooled tadalafil 5/10/20mg as-needed regimen. The CHMP however noted that the inclusion of high proportion of responders to tadalafil/PDE5 inhibitors in the 'once-a day' studies as well as the higher dose of 20 mg available for the 'as needed' regimen may have contributed to such lower incidences of AEs.

Although the comparison of the safety profile across different studies may have several limitations, the CHMP was of the opinion that safety profile of both dosing regimens seemed in overall to be comparable.

A slightly higher incidence of ECG abnormalities such as supraventricular rhythm disorders, ST and T wave abnormalities and other rhythm disorders, mainly sinus bradycardia, were reported in patients treated with tadalafil as compared to placebo. However, a clear dose-response relationship could not be established.

Analysis of the reported cases of dizziness in subjects older than 65 years of age did not reveal evidence of hypotensive events.

There were no clinically meaningful differences in the adverse event profile between subjects with or without diabetes, subjects with or without hypertension, or subjects with or without cardiovascular disease in the 'once-a-day' dosing studies.

5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: The MAH has committed to update the RMP to include the need to focus on the safety profile in elderly patients on a daily dose treatment.

6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Cialis 2.5 mg and 5 mg film-coated tablets are prepared by standard manufacturing methods. The development, manufacture and quality control of the finished product is well defined and controlled. The quality of the excipients and of the primary packaging remains unchanged compared to the already authorised finished products. All relevant quality characteristics of the finished product (release and shelf-life) are specified. The proposed limits are sufficient. The analytical methods used are described and validated adequately.

Non-clinical pharmacology and toxicology

Previously submitted non clinical data for the current approved formulations were considered relevant to tadalafil 2.5 mg and 5 mg film-coated tablets to characterise the pharmacological properties and toxicological profile of these new strengths.
Based on the submitted non clinical data, the CHMP considered that the toxicological profile of tadalafil 2.5 mg and 5 mg film coated tablets has been adequately addressed. Nevertheless, a concern was raised related to the lack of long-term toxicity data in fish. To address this issue, the MAH committed to conduct a standard early life stage study in fathed minnows (OECD Guideline 210) as a follow up measure, the study being initiated around Q3/2007.

Efficacy

The clinical data provided by the applicant are considered sufficient to support the extension application for the 2 new doses of 2.5 and 5 mg, in responder patients who anticipate a frequent use of Cialis (i.e. at least twice weekly). Detailed information has been reflected in section 4.2 of the SPC.

Safety

The safety profile of the 2 new doses (2.5 and 5 mg) for Cialis to be used as ‘once a day’ regimen was similar to that of the current approved doses 10 and 20 mg to used as ‘on demand’ regimen. Based on data collected to date, the safety profile appeared favourable.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Risk-benefit assessment and recommendation

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that: the following additional risk minimisation activities were required: The MAH has committed to update the RMP to include the need to focus on the safety profile in elderly patients on a daily dose treatment.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Cialis in the treatment of erectile dysfunction was favourable and therefore recommended the extension of the marketing authorisation.