26 January 2017
EMA/CHMP/23344/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tadalafil Lilly

International non-proprietary name: tadalafil

Procedure No. EMEA/H/C/004666/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Tadalafil Lilly
Applicant:	Eli Lilly Nederland B.V. Papendorpseweg 83 3528 BJ Utrecht NETHERLANDS
Active substance:	TADALAFIL
International Non-proprietary Name/Common Name:	tadalafil
Pharmaco-therapeutic group (ATC Code):	urologicals, drugs used in erectile dysfunction (G04BE08)
Therapeutic indication(s):	Treatment of erectile dysfunction in adult males. In order for tadalafil to be effective, sexual stimulation is required. Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males (for the 5mg strength only).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	2.5 mg, 5 mg, 10 mg and 20 mg
Route(s) of administration:	Oral use
Packaging:	Blister (alu/PVC)
Package size(s):	12 tablets, 14 tablets, 2 tablets, 28 tablets, 4 tablets, 8 tablets and 84 tablets

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 2 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Tadalafil Lilly, through the centralised procedure. As this application concerns active substance already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 13 October 2016.

The applicant applied for the following indications:

- Treatment of erectile dysfunction in adult males.

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

- Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males (for the 5mg strength only).

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Eli Lilly Nederland B.V. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Cialis authorised on 12 November 2002in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Bruno Sepodes

PRAC Rapporteur: Dolores Montero Corominas

- The application was received by the EMA on 2 November 2016.
- The procedure started on 28 November 2016.
- The CHMP and PRAC Rapporteurs' joint Assessment Report was circulated to all CHMP members on 3 January 2017.
- During the PRAC meeting on 12 January 2017, endorsed the relevant sections of the joint CHMP/PRAC Assessment Report.
- The CHMP and PRAC Rapporteurs' updated joint Assessment Report was circulated to all CHMP members on 20 January 2017.
- The CHMP and PRAC Rapporteurs' revised updated joint Assessment Report was circulated to all CHMP members on 24 January 2017.
- During the meeting on 26 January 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tadalafil Lilly.

2. Scientific discussion

2.1. Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

The MAH for Cialis, has provided consent to make use of the pharmaceutical, preclinical and clinical documentation contained in the file of Cialis, assessed and approved. As a consequence, quality, safety and efficacy of Tadalafil Lilly are identical to the up to date quality, safety and efficacy profile of Cialis.

The application for Tadalafil Lilly concerns the strengths of 2.5 mg, 5 mg, 10 mg and 20mg film-coated tablets and consists only of Module 1 information.

The benefit-risk of Tadalafil Lilly is considered to be positive, as it is a duplicate of Cialis, for which the B/R is positive in the following indications:

- Treatment of erectile dysfunction in adult males for Cialis 2.5 mg, 5 mg, 10 mg and 20mg film-coated tablets.
- Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males for Cialis 5 mg film-coated tablets.

Tadalafil is an orally administered phosphodiesterase type 5 (PDE5) inhibitor of cyclic guanosine monophosphate (cGMP)-specific PDE5. As a treatment for erectile dysfunction, when sexual stimulation

causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

This effect is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced.

2.2. Quality aspects

Since this application is an informed consent of the Cialis application, the quality data in support of the Tadalafil Lilly application are identical to the up-to-date quality data of the Cialis dossier, which has been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

2.3.1. Introduction

Since Tadalafil Lilly application is an informed consent of Cialis application, the non-clinical data in support of Tadalafill Lilly application is identical to the up-to-date non-clinical data of the Cialis dossier which has been assessed and approved (including all post-marketing procedures).

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant has provided an ERA, comprising an estimation of exposure (Phase I) and an initial environmental fate and effects analysis (Phase II, Tier A) for tadalafil. Since in Tier A a potential risk for the medicinal product to the environment has not been identified, a Phase II Tier B assessment does not need to be conducted. Moreover, tadalafil is not classified as a PBT drug substance, although temperature adjusted DT50 values in aquatic sediment systems met the criteria for very persistent (vP). The company included in SmPC 6.6 the statement: Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This was considered acceptable by the CHMP.

Considering the above tadalafil is not expected to pose a risk to the environment.

Table 1. Summary of main study results for tadalafil

Substance (INN/Invented Name): tadalafil			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117 …	2.32	Potential PBT No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.32	not B
Persistence	DT50 or ready	DT50 = 9 days	not P

	biodegradability	4.9% $^{14}CO_2$ evolution			
Toxicity	NOEC or CMR	480 µg/L (*D. magna*, OECD 211) 2000 µg/L (*D. magna*, OECD 202) 2100 µg/L (*O. mykiss*, FDA 4.11) 300 µg/L (yield) (*P. subcapitata* OECD 201) 1200 µg/L (rate) (*P. subcapitata* OECD 201) 1200 µg/L (*P. promelas*, OECD 210) 125000 µg/kg (*C. riparius*, OECD 218)			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.325	µg/L			> 0.01 threshold (Yes)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	Log Koc = 1.95			
Biodegradability Test in Sludge	OECD 302A	Not readily Biodegradable			< 10% evolution of radiolabeled carbon over 28 days when ^{14}C-tadalafil was incubated with a concentrated inoculum of sewage sludge microorganisms
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	300 (yield) 1200 (rate)	µg/L	Species: *Pseudokirchneriella subcapitata*
Water Flea, Reproduction Test	OECD 211	NOEC	480	µg/L	Species: *Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	1200	µg/L	Species: Fathead Minnow - *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000000	µg/L	

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered there were no non-clinical objections to the granting of the authorisation of this informed consent application for Tadalafil Lilly.

2.4. Clinical aspects

Since Tadalafil Lilly application is an informed consent of Cialis application, the clinical data in support of the Tadalafil Lilly application are identical to the up-to-date clinical data of Cialis dossier, which have been assessed and authorised (including all post-marketing procedures).

2.5. Risk management plan

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	<u>All Indications:</u> • Hypotension/Increased Hypotensive Effect • Priapism
Important Potential Risks	<u>All Indications:</u> • Nonarteritic anterior ischemic optic neuropathy (NAION) • Sudden hearing loss <u>PAH Indication</u>: • Increased Uterine Bleeding
Important Missing Information	<u>Tadalafil Once-a-Day ED and BPH Indications:</u> • Characterization of adverse events in elderly patients (≥65 years of age)

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
H6D-MC-LVHQ: A Prospective Case-Crossover Study to Evaluate the Possible Association Between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION) Category 3	Study H6D-MC-LVHQ is an observational, prospective, case crossover study aiming to examine the possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult male subjects (approximately 125 NAION cases will be included).	The possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult male subjects	Study ongoing	Estimated completion date Q2 2016 The final study report will be submitted with PSUR (reporting period 16 October 2015 to 15 October 2016). If there is important new safety information affecting the benefit risk of tadalafil, the study report and corresponding documents will be submitted earlier in accordance with the regulations.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypotension/Increased Hypotensive Effect	• Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that ADCIRCA is contraindicated in patients using any form of organic nitrate, or who have hypotension (<90/50mmHg) or uncontrolled hypertension. Package leaflet states that ADCIRCA should not be taken if already taking nitrates or if they have low blood pressure. • Specific label updates to the SmPC have been proposed stating that the combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is not recommended. The regulatory procedure is ongoing. • Specific label text in the SmPC under Section 4.4 (Special warnings and precautions) describing the risk of hypotension with tadalafil. • Specific label text in the SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) for nitrates, anti-hypertensives, and alcohol. • Hypotension has been listed as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet instructs patients to tell the doctor if they are taking alpha-blockers. • The package leaflet under Possible Side Effects (Section 4) includes low blood pressure	None
Priapism	• Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. • Priapism and Prolonged erections are listed in the SmPC as undesirable effects under Section 4.8. • The package leaflet instructs patients to inform the doctor immediately if the erection lasts continuously for more than 4 hours and instructs patients to inform their doctor before taking ADCIRCA if they have any deformation of the penis.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks		
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)	• Specific label text in the SmPC under Section 4.3 (Contraindications) indicates that ADCIRCA is contraindicated in patients who have loss of vision in one eye because of NAION. • Specific label text in the SmPC under Special Warnings and Precautions (Section 4.4) states that visual defects and cases of NAION have been reported in connection with the intake of ADCIRCA and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect he should stop taking ADCIRCA and consult a physician immediately. • NAION has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet, instructs patients not to take ADCIRCA if they have ever had loss of vision because of NAION • The package leaflet under Possible Side Effects (Section 4) includes partial, temporary or permanent decrease or loss of vision in one or both eyes	None
Sudden Hearing Loss	• Sudden hearing loss has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet includes this risk of sudden hearing loss.	None
Increased Uterine Bleeding	• Increased uterine bleeding has been listed in the SmPC as an adverse reaction under Section 4.8 (Undesirable effects). • The package leaflet includes this risk of increase uterine bleeding.	None

RMP version 7.1 refers to both Adcirca and Cialis/Tadalafil Lilly. However, Tadalafil Lilly is not indicated for the treatment of pulmonary arterial hypertension and such risks do not apply.

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.1 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

Since Tadalafil Lilly application is an informed consent of Cialis application, the product information (PI) for Tadalafil Lilly 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets is identical to the up-to-date PI of Cialis, with the only exception of the name of the medicinal product.

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-risk balance

Tadalafil Lilly film-coated tablets are identical to Cialis film-coated tablets, the CHMP has previously reviewed data on quality, safety and efficacy of Cialis and considered the benefit/risk balance favourable.

Therefore recommended the granting of the marketing authorisation for the following indications:

- Treatment of erectile dysfunction in adult males.
  In order for tadalafil to be effective, sexual stimulation is required.
  Tadalafil Lilly is not indicated for use by women.

- Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy and in accordance with the originator Cialis, the CHMP considers by consensus that the benefit-risk balance of Tadalafil Lilly is favourable in the following indication:

For Tadalafil Lilly 2.5 mg, 5 mg, 10 mg and 20 mg film-coated tablets:

Treatment of erectile dysfunction in adult males.

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

Tadalafil Lilly is not indicated for use by women.

For Tadalafil Lilly 5 mg film-coated tablets:

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.