IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Cialis for men 10 mg film-coated tablets
Tadalafil
PA25208/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Cialis for men 10 mg film-coated tablets, from A. Nattermann & Cie. GmbH on 1st December 2023 for:

Treatment of erectile dysfunction in adult males.

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

Cialis for Men 10 mg Film-coated tablet is not indicated for use by women.

This Marketing Authorisation Application (MAA) for Cialis for men 10 mg film-coated tablets (tadalafil) as a non-prescription medicine in the treatment of erectile dysfunction (ED) for use in adult males was submitted in accordance with Article 10(3) of Directive 2001/83/EC. The reference product is Cialis 10 mg film-coated tablets registered via Centralised Procedure since 12/11/2002.

This application was submitted via decentralised procedure with Ireland as Reference Member State (RMS) and Norway as Concerned Member State (CMS).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product:	Cialis for men 10 mg Film-coated tablets
Name(s) of the active substance(s) (INN)	Tadalafil
Pharmacotherapeutic classification (ATC code)	G04BE08
Pharmaceutical form and strength(s)	10 mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA25208/001/001
Marketing Authorisation Holder	A. Nattermann & Cie. GmbH
MRP/DCP No.	IE/H/1194/001/DC
Reference Member State	IE
Concerned Member State	NO

II. QUALITY ASPECTS

II.1. Introduction

This application is for Cialis for men 10 mg film-coated tablets.

II.2 Drug substance

The active substance is Tadalafil, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Cialis for men 10 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a hybrid formulation of Cialis 10 mg film-coated tablets on the European market since 2002. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

No new nonclinical pharmacology studies have been provided. Tadalafil is a well-known active substance and its function as a PDE5 inhibitor in the treatment of erectile dysfunction is clinically well characterised. Therefore, the absence of new pharmacology studies for this hybrid application is acceptable.

III.3 Pharmacokinetics

The absorption, distribution, metabolism, and excretion of tadalafil has been previously characterised in rats, mice, and dogs. No new nonclinical pharmacokinetic studies have been performed for this MAA. This is acceptable for a hybrid" under article 10(3) of Directive 2001/83/EC as amended.

III.4 Toxicology

No new nonclinical toxicology studies were performed to support this application and reference is made to the nonclinical studies performed to support the authorisation of the reference product. This is acceptable for a hybrid application under Article 10(3) of Directive 2001/83/EC as amended. The safety profile of tadalafil is well characterised clinically and the MDD of 10 mg dose for this product is lower than the MDD of 20 mg in the reference product.

III.5 Ecotoxicity/environmental risk assessment

The PEC for non-prescription tadalafil 10 mg film-coated tablet in surface water (PECsurfacewater) was calculated at 0.050 µg/L according to the Phase I calculation of PEC as given by the 2006 CHMP ERA guideline and using the default values for penetration factor (Fpen, 1% of the total population), amount of wastewater per inhabitant per day (200 L), and dilution factor.

Because the Phase I calculation of PECsurfacewater using the default values is greater than the 0.01 mg/L action limit, a Phase IIA initial environmental and effect analysis on the aquatic compartment was performed.

Summary of main study results

Substance (INN/Invented Name): Tadalafil					
CAS-number (if available): 171596-29-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	2.32			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.05	mg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	*Log* K_{oc} =1.95			
Inherent Biodegradability Test	OECD 302A	DT_{50} = 9 days 4.9% $^{14}CO_2$ evolution			
Sludge adsoprtion	OECD 302A	Kd = 183 to 644 Koc = 599 to 2100 Average Koc = 1183			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =3.8 to 4.6 days $DT_{50,\ water/sediment}$ = 70 to 117 days 1.8 to 3.4 % $^{14}CO_2$ evolution			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth	OECD 201	NOEC	300	µg/L	*Pseudokirchneriella*

Inhibition Test/*Species*					*subcapitana*
Daphnia sp. Reproduction Test	OECD 211	NOEC	480	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1200	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	1000	mg/L	
Sediment dwelling organism	OECD 218	NOEC	125	mg/kg	*Chironomus riparius*

Conclusions on studies:

Tadalafil is not a PBT substance.
- Considering the above data, tadalafil is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

No new nonclinical studies were performed to support this application and reference is made to the nonclinical studies performed to support the authorisation of the reference product which is acceptable. The nonclinical sections of the SmPC are in-line with the reference product. The MAA is approvable from a nonclinical perspective.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tadalafil is a well-known active substance with established efficacy and tolerability.

For this Marketing Authorisation Application (MAA) for tadalafil 10 mg film-coated tablets as a non-prescription medicine in the treatment of erectile dysfunction (ED) for use in adult males, only one dose and strength (10mg) is proposed.

Cialis for Men 10 mg Film-coated tablet is identical to the reference medicinal product (Cialis 10 mg film-coated tablets from Eli Lilly and Company registered through a Centralised Procedure since 12/11/2002) and therefore, no bioequivalence study has been conducted.

The content of the SmPC approved during the decentralised procedure is closely aligned to the reference medicinal product but adapted where needed to cater for the non-prescription legal status.

A Risk Management Plan has been submitted.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.2 Pharmacokinetics

Absorption
Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus Cialis for Men 10 mg Film-coated tablet may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 l, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function. Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects. 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).

IV.3 Pharmacodynamics

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). 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.

IV.4 Clinical Efficacy

No new efficacy studies have been performed. The Applicant has adequately reviewed and discussed the clinical studies and literature data in support of the efficacy of 10mg tadalafil for the proposed indication. The proposed 10 mg strength is in line with one of the strengths of the reference medicinal product and is also the dose that is generally recommended as per the reference medicinal product SmPC. The clinical data and the literature review data also support the efficacy advantage of tadalafil 10 mg compared with 5 mg generally and on an as-needed basis.

IV.5 Clinical Safety

No new safety studies have been performed. The clinical safety profile of tadalafil as a treatment for erectile dysfunction in adult males is well-known with over 20 years of clinical experience and wide use. To further substantiate this, the Applicant refers to safety data from the clinical development program, post-marketing pharmacovigilance and surveillance activities.

The reported post-marketing experience with prescription tadalafil is similar to the safety profile derived from the development clinical studies. The proposed SmPC warns accordingly.

For events related to important identified and potential risks of tadalafil, the product information, Pharmacy guide and checklist warn accordingly.

Risk Management Plan (RMP)
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cialis for Men 10 mg Film-coated tablet.

Summary table of safety concerns in approved RMP:

Important identified risks	• Hypotension/increased hypotensive effect • Priapism
Important potential risks	• Sudden hearing loss • Non-arteritic anterior ischemic optic neuropathy (NAION)

	• Serious cardiovascular events associated with sexual activity in men with pre-existing or undiagnosed cardiovascular disease and/or risk factors[a]
Missing information	• None

[a] Safety concerns for non-prescription use.

Summary table of pharmacovigilance activities and risk minimisation measures by safety concern:

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hypotension/increased hypotensive effect	**Routine risk minimization measures:** SmPC sections 4.3, 4.4, 4.5 and 4.8 PIL sections 2 and 4 Labelling section 15 (safety messages on the outer-pack providing instructions on safe use) **Additional risk minimization measures (in countries where they are required):** Guide for pharmacists/pharmacy staff Checklist for pharmacists/pharmacy staff or customers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Priapism	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 **Additional risk minimization measures (in countries where they are required):** Guide for pharmacists/pharmacy staff Checklist for pharmacists/pharmacy staff or customers.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Sudden hearing loss	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 **Additional risk minimization measures (in countries where they are required):** Guide for pharmacists/pharmacy staff Checklist for pharmacists/pharmacy staff or customers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Non-arteritic Anterior ischemic optic neuropathy (NAION)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 **Additional risk minimization measures (in countries where they are required):** Guide for pharmacists/pharmacy staff Checklist for pharmacists/pharmacy staff or customers	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Serious cardiovascular events associated with sexual activity in men with pre-existing or undiagnosed cardiovascular disease and/or risk factors	**Routine risk minimization measures:** SmPC section 4.3 and 4.4 PIL section 2 Labelling section 7 (other special warnings, if necessary) and 15 (safety messages on the outer-pack providing instructions on safe use) **Additional risk minimization measures (in countries where they are**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	required): Guide for pharmacists/pharmacy staff Checklist for pharmacists/pharmacy staff or customers	

Periodic Safety Update Reports (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This Marketing Authorisation Application (MAA) for Cialis for Men 10 mg film-coated tablets (tadalafil) as a non-prescription medicine in the treatment of erectile dysfunction (ED) for use in adult males was submitted in accordance with Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Cialis 10 mg film-coated tablets registered via Centralised Procedure since 12/11/2002.

V. OVERALL CONCLUSIONS

Tadalafil is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Cialis for men 10 mg film-coated tablets are identical to the reference medicinal product (Cialis 10 mg film-coated tablets from Eli Lilly and Company) and therefore, no bioequivalence study has been conducted.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Cialis for men 10 mg film-coated tablets demonstrated bioequivalence with the reference medicinal product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

11.10.2023