Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Tadalafil 10 mg and 20 mg Film-coated Tablets

(Tadalafil)

Licence Number: PL 06464/3092-3

Waymade Plc Trading as Sovereign Medical

LAY SUMMARY

Tadalafil 10 mg and 20 mg Film-coated Tablets (Tadalafil)

This is a summary of the Public Assessment Report (PAR) for Tadalafil 10 mg and 20 mg Film-coated Tablets (PL 06464/3092-3). It explains how Tadalafil 10 mg and 20 mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Tadalafil 10 mg and 20 mg Film-coated Tablets.

The products will be collectively referred to as Tadalafil film-coated tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Tadalafil film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Tadalafil film-coated tablets and what are they used for?
Tadalafil film-coated tablets are 'generic medicines'. This means that Tadalafil film-coated tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Cialis 10 mg and 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands).

Tadalafil is a treatment for adult men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity. Tadalafil has been shown to significantly improve the ability of obtaining a hard erect penis suitable for sexual activity.

How do Tadalafil film-coated tablets work?
Tadalafil film-coated tablets contain the active substance tadalafil which belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation tadalafil works by helping the blood vessels in the patient's penis to relax, allowing the flow of blood into their penis. The result of this is improved erectile function. Tadalafil will not help the patient if they do not have erectile dysfunction.

It is important to note that tadalafil does not work if there is no sexual stimulation. The patient and their partner will need to engage in foreplay, just as they would if they were not taking a medicine for erectile dysfunction.

How are Tadalafil film-coated tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

Tadalafil film-coated tablets are for oral use in men only. The whole tablet must be swallowed with some water. The tablets can be taken with or without food.

The recommended starting dose is one 10 mg tablet before sexual activity. If the effect of this dose is too weak a doctor may increase the dose to 20 mg.

Drinking alcohol may affect the patient's ability to get an erection and may temporarily lower the patient's blood pressure. If the patient has taken or is planning to take this medicine, they should avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up.

It is important to note that tadalafil does not work if there is no sexual stimulation. The patient and their partner will need to engage in foreplay, just as they would if they were not taking a medicine for erectile dysfunction.

The patient may take a Tadalafil film-coated tablet at least 30 minutes before sexual activity.

Tadalafil may still be effective up to 36 hours after taking the tablet. This medicine must not be taken more than once a day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not recommended for continuous daily use.

This medicine can only be obtained with a prescription.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Tadalafil film-coated tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Tadalafil film-coated tablets have been shown in studies?
Because Tadalafil film-coated tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine, Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Tadalafil film-coated tablets?
Because Tadalafil film-coated tablets are generic medicines and are bioequivalent to the reference medicine Cialis 20 mg tablets (Eli Lilly Nederland B.V., The Netherlands), their possible side effects are taken as being the same as those for the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Tadalafil film-coated tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Tadalafil film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Tadalafil film-coated tablets have been shown to have comparable quality and to be bioequivalent to Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands). Therefore, the MHRA decided that, as for Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands); the benefits are greater than the risks and recommended that Tadalafil film-coated tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Tadalafil film-coated tablets?
A risk management plan (RMP) has been developed to ensure that Tadalafil film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflet for Tadalafil film-coated tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Tadalafil film-coated tablets

Marketing Authorisations were granted in the UK on 14 June 2017.

The full PAR for Tadalafil film-coated tablets follows this summary.

This summary was last updated in July 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Waymade Plc Trading as Sovereign Medical, Marketing Authorisations for the medicinal products, Tadalafil 10 mg and 20 mg film-coated tablets (PL 06464/3092-3). The products are prescription-only medicines (POM) indicated for treatment of erectile dysfunction in adult males. In order for tadalafil to be effective, sexual stimulation is required. Tadalafil is not indicated for use by women.

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Cialis 10 mg and 20 mg film-coated tablets which were first authorised to Eli Lilly Nederland B.V., The Netherlands on 12 November 2002 via the centralised procedure.

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 treatment of erectile dysfunction in the absence of sexual stimulation.

With the exception of two bioequivalence studies, no new clinical data were provided with these applications. The bioequivalence studies were submitted to support these applications, comparing the applicant's test product Tadalafil 20 mgTablets with the reference product Cialis® 20 mg film-coated tablets (Eli Lilly Nederland B.V.,) in healthy, adult male, human subjects under fasting and fed conditions. The bioequivalence studies were conducted in line with current Good Clinical Practice (GCP).

No new non-clinical studies were submitted, which is acceptable given that the applications are generic medicinal products of originator products that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tadalafil 10 mg and 20 mg film-coated tablets outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

The proposed formulation is a film-coated tablet and each film-coated tablet contains 10 mg or 20 mg tadalafil as the active ingredient. The excipients present are lactose monohydrate, croscarmellose sodium, povidone K-25, hydroxy propyl cellulose, magnesium stearate, colloidal silicone dioxide and sodium laurilsufate making up the film-coating, and hypromellose, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of yellow iron oxide (E172) which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

The tablets are packaged either in oriented polyamide (OPA)/aluminium/ polyvinylchloride (PVC)/aluminium blisters or PVC/ACLAR/aluminium blisters containing a pack size of 4 film-coated tablets.

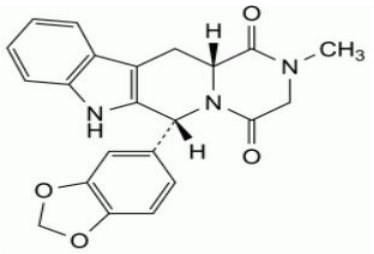
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Tadalafil

Chemical name: (6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]-pyrido[3,4-*b*]indole-1,4-dione.

Structural formula:



Molecular formula: $C_{22}H_{19}N_3O_4$

Molecular mass: 389.4 g/mol

Appearance: White or almost white powder.

Solubility: Practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride.

Tadalafil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, tadalafil, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious film-coated tablets containing 10 mg or 20 mg tadalafil per tablet, that are generic versions of the reference products Cialis® 10 mg and 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated at commercial scale batch size and have shown satisfactory results.

Finished Product Specifications

The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of tadalafil are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Tadalafil 10 mg and 20 mg film-coated tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of tadalafil is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of tadalafil.

Based on the data provided, Tadalafil film-coated tablets can be considered bioequivalent to Cialis® 10 mg and 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1

An open label, balanced, randomised, two-treatment, two-sequence, two period, single-dose, crossover oral bioequivalence study of the applicant's test product Tadalafil 20 mg Tablets versus the reference product Cialis® 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands) in healthy adult subjects under fasting conditions.

Subjects were administered a single oral dose (1 x 20 mg tablet) of the test or reference product with 250 mL of water after an overnight fast of at least 10 hours before study drug administration in each study period.

Blood samples were collected for plasma levels before dosing and up to and including 96 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

Results

Table 1: Summary statistics for the pharmacokinetic parameters for tadalafil is presented below:

Table - 1: The results of log transformed PK Parameters of Tadalafil are tabulated below.

PK Parameters	Least square Geometric mean		Ratio T/R (%)	90% Confidence Intervals		Intra Subject CV%	Power %
	T	R					
C_{max} (ng/mL)	365.4732	365.9949	99.86	94.16	105.90	14.10	100.00
AUC_{0t} (ng.hr/mL)	11651.1061	11539.1727	100.97	94.72	107.63	15.34	99.99

Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for tadalafil lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands) under fasting conditions.

STUDY 2

An open label, balanced, randomized, two-treatment, two-sequence, two period, single-dose, crossover oral bioequivalence study of the applicant's test product Tadalafil 20 mgTablets versus the reference product Cialis® 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands) in healthy adult subjects under fed conditions.

Subjects were administered a single oral dose (1 x 20 mg tablet) of the test or reference product with 240 mL of water after an overnight fast of at least 10 hours and a standardized high-fat, high-calorie meal 30 minutes before study drug administration in each study period.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Table 2: Summary statistics for the pharmacokinetic parameters for tadalafil is presented below:

PK Parameters	Least square Geometric mean		Ratio T/R (%)	90% Confidence Intervals		Power %	Intra Subject CV%
	T	R					
C_{max} (ng/mL)	403.8967	376.1685	107.37	101.49	113.59	100.00	13.55
AUC_{0-72h} (ng.hr/mL)	10719.7154	10606.7019	101.07	96.51	105.84	100.00	11.09

Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for tadalafil lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Cialis 20 mg film-coated tablets (Eli Lilly Nederland B.V., The Netherlands) under fed conditions.

As the 10 mg and 20 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 20 mg tablet strength can be extrapolated to the 10 mg strength tablet.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), 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 Tadalafil 10 mg and 20 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Priapism	Included in SmPC sections 4.4, 4.8 Included in PIL section 4	None
Hypotension/increased hypotensive effect	Included in SmPC sections 4.3, 4.4, 4.5, 4.8 Included in PIL sections 2, 3, 4	None
Important Potential Risks		
Non-arteritic anterior ischaemic optic neuropathy (NAION)	Included in SmPC sections 4.3, 4.4, 4.8 Included in PIL sections 2, 4	None
Sudden hearing loss	Included in SmPC section 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Included in PIL section 4	
Important missing information		
Use in elderly patients	Included in SmPC sections 4.2, 4.5, 4.8, 5.2	None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

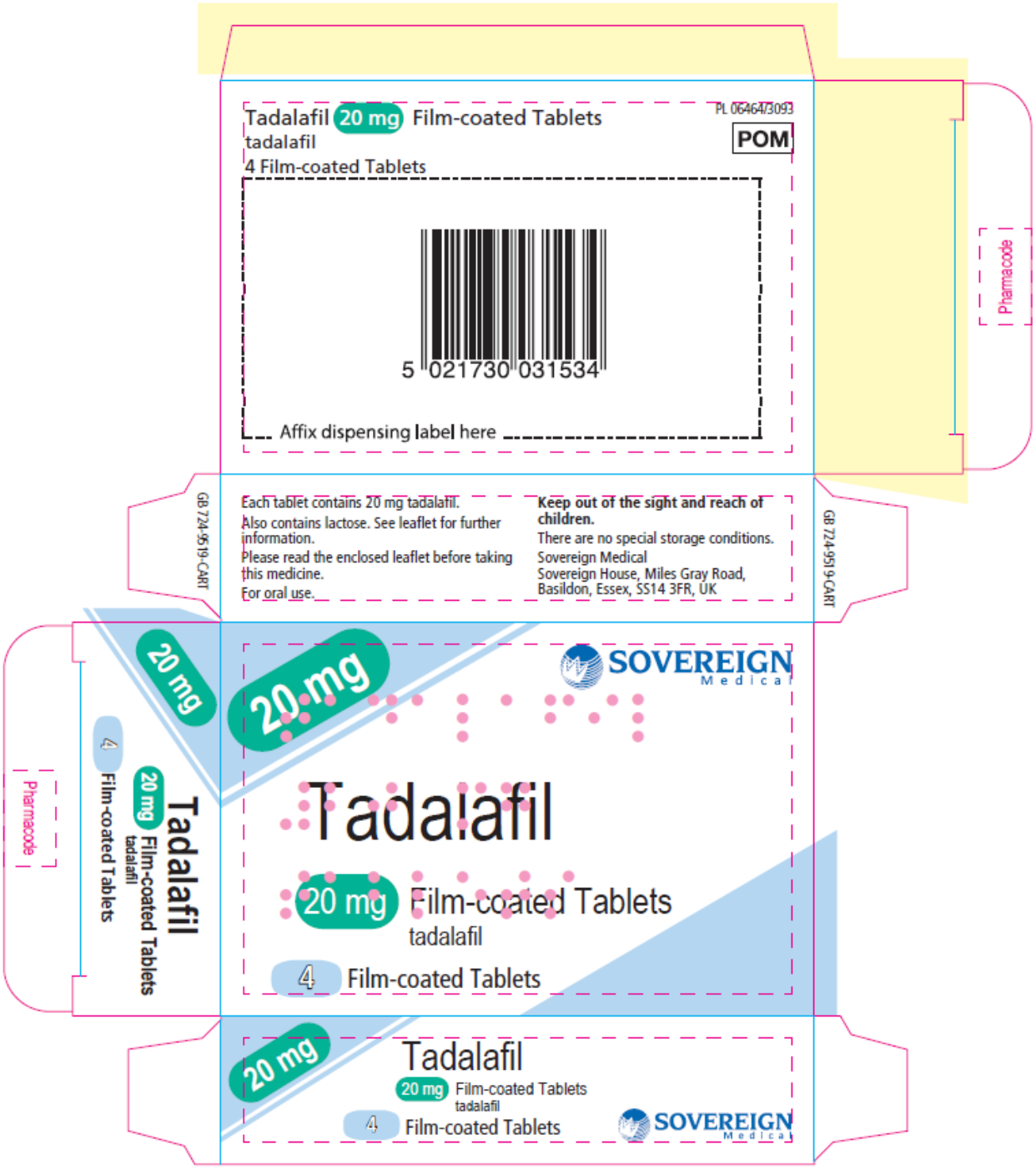
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tadalafil is considered to have demonstrated the therapeutic value of the compound. The proposed products are bioequivalent to the reference products. The benefit-risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Tadalafil 10 mg and 20 mg Film-coated Tablets is presented below:


Tadalafil 10 mg
Film-coated Tablets
tadalafil
Sovereign Medical
GB 724-9485-FOIL


Tadalafil 20 mg Film-coated Tablets
tadalafil
4 Film-coated Tablets
PL 06464/3093
POM
5 021730 031534
Affix dispensing label here
Pharmacode
Each tablet contains 20 mg tadalafil.
Also contains lactose. See leaflet for further information.
Please read the enclosed leaflet before taking this medicine.
For oral use.
Keep out of the sight and reach of children.
There are no special storage conditions.
Sovereign Medical
Sovereign House, Miles Gray Road,
Basildon, Essex, SS14 3FR, UK
GB 724 9519 CART
20 mg
SOVEREIGN Medical
Tadalafil
20 mg Film-coated Tablets
tadalafil
4 Film-coated Tablets
Tadalafil
20 mg Film-coated Tablets
tadalafil
4 Film-coated Tablets


Tadalafil 20 mg
Film-coated Tablets
tadalafil
Sovereign Medical
GB 724-9493-FOIL

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)