Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Vardenafil 5, 10 and 20 mg tablets

(vardenafil hydrochloride)

UK licence Number: PL 33155/0062-0064

Rivopharm UK Ltd

LAY SUMMARY
Vardenafil 5, 10 and 20mg tablets
(vardenafil hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Vardenafil 5, 10 and 20mg tablets (PL 33155/0062-0064). This summary explains how Vardenafil 5, 10 and 20mg tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

The products will be collectively referred to as Vardenafil Tablets throughout the remainder of this lay summary.

For practical information about using Vardenafil Tablets , patients should read the package leaflet available on the MHRA website or contact their doctor or pharmacist.

What are Vardenafil Tablets and what are they used for?

Vardenafil Tablets are 'generic medicines'. This means that Vardenafil Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Levitra 5, 10 and 20mg film coated tablets, which are currently granted Marketing Authorisations to Bayer Pharma AG.

Vardenafil Tablets are used for the treatment of erectile dysfunction in adult men, a condition which implies difficulties in getting or keeping an erection.

At least one in ten men has trouble getting or keeping an erection at some time. There may be physical or psychological causes, or a mixture of both. Whatever the cause is, due to muscle and blood vessel changes not enough blood stays in the penis to make it hard and keep it hard.

How do Vardenafil Tablets work?

Vardenafil Tablets contain the active ingredient vardenafil, which belongs to a member of a class of medicines called phosphodiesterase type 5 inhibitors. This medicine reduces the action of the natural chemical in the body which makes erections go away. Vardenafil Tablets allows an erection to last long enough to satisfactorily complete sexual activity. Vardenafil Tablets will only work when a patient is sexually stimulated.

How are Vardenafil Tablets used?

The pharmaceutical form of this medicine is a tablet and the route of administration is oral. One Vardenafil Tablet should be swallowed with a glass of water. Vardenafil Tablets must not be taken more than once a day.

This medicine should be taken exactly as advised by the patient's doctor or pharmacist. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose is 10mg. Vardenafil Tablets should be taken about 25 to 60 minutes before sexual activity. With sexual stimulation, a patient may achieve an erection anywhere from 25 minutes up to four to five hours after taking Vardenafil Tablets.

The patient should tell their doctor if they think that Vardenafil Tablets, are too strong or too weak. The doctor may suggest a switch to a different dose, depending on how well it works for a patient.

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

The medicine can only be obtained with a prescription.

What benefits of Vardenafil Tablets have been shown in studies?
Because Vardenafil Tablets are generic medicines, studies in people have been limited to tests to determine that the medicines are bioequivalent to the reference products Levitra 5, 10 and 20mg film coated tablets (Bayer Pharma AG). Two medicines are bioequivalent when they produce similar levels of active substance in the body.

What are the possible side effects of Vardenafil Tablets?
Because Vardenafil Tablets are generic medicines, their possible side effects are taken as being the same as those of the reference products, Levitra 5, 10 and 20mg film coated tablets (Bayer Pharma AG).

For the full list of all side effects reported with Vardenafil Tablets, see Section 4 of the package leaflet available on the MHRA website.

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

Why are Vardenafil Tablets approved?
It was concluded that, in accordance with EU requirements, Vardenafil Tablets have been shown to have comparable quality and to be bioequivalent to Levitra 5, 10 and 20mg film coated tablets. Therefore, the MHRA considered that, as for the reference medicines, Levitra 5, 10 and 20mg film coated tablets, the benefits are greater than the risks and recommended that Vardenfil Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Vardenafil Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Vardenafil Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet of Vardenafil Tablets, including the appropriate precautions to be followed by 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 Vardenafil Tablets
The UK granted Marketing Authorisations for Vardenafil Tablets on 10 November 2017.

The full PAR for Vardenafil Tablets follows this summary.

This summary was last updated in December 2017.

SCIENTIFIC DISCUSSION

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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 Rivopharm UK Ltd Marketing Authorisations for the medicinal product Vardenafil 5, 10 and 20mg tablets (PL 33155/0062-0064) on 10 November 2017.

These products are prescription-only medicines (legal classification POM) used for the treatment of erectile dysfunction in adult men. Erectile dysfunction is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Levitra 5, 10 and 20mg film coated tablets (EU/1/03/248/001-03), which were granted a licence to Bayer Pharma AG on 6 March 2003.

Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is released in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

The applicant has submitted a bioequivalence study comparing the test product Vardenafil 20mg Tablets with the reference product Levitra 20 mg tablets (Bayer Pharma AG) in healthy subjects under fasting conditions

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture and assembly of these products.

A satisfactory summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) has been provided with these applications.

II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as film-coated tablets containing 5mg, 10mg and 20 mg vardenafil as vardenafil hydrochloride, as the active ingredient.

Other ingredients consist of the following pharmaceutical excipients: cellulose microcrystalline, crospovidone, silica colloidal anhydrous, aspartame (E951), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172) and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide red (E172) and iron oxide yellow (E172) which comply with a national formulary (NF). Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used contain material of animal or human origin. Confirmation has 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 products.

The finished products are packaged into aluminium/aluminium blisters. The pack sizes are 2, 4, 8, 12 or 20 tablets. Not all pack sizes may be marketed.

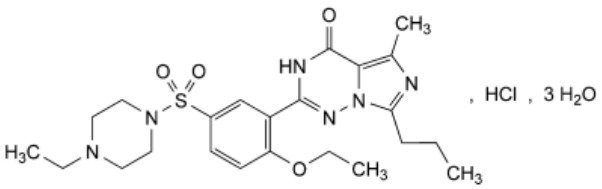
Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

II.2. Drug Substance

INN: Vardenafil hydrochloride

Chemical name: 2-[2-ethoxy-5-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one hydrochloride trihydrate

Structural formula:



Molecular formula:	$C_{23}H_{33}ClN_6O_4S.3H_2O$
Molecular mass:	579.1 g/mol
Appearance:	White or slightly brown or yellow powder.
Solubility:	Slightly soluble in water, freely soluble in anhydrous ethanol and practically insoluble in heptane.

Vardenafil hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, vardenafil hydrochloride, are covered by the 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, stable products that can be considered generic products of the reference products Levitra 5, 10 and 20 mg film coated tablets. A satisfactory account of the pharmaceutical development has been provided.

Comparable *in vitro* dissolution profiles have been provided for the test and reference products.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of each product strength, together with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale for each strength and has shown satisfactory results.

Finished Product Specifications

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

Stability of the Product

Finished product stability studies were performed on batches of finished products in the packaging proposed for marketing in accordance with current guidelines. The data from these studies support a shelf-life of 2 years. These medicinal products do not require any special storage conditions.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these products from a pharmaceutical perspective.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of vardenafil hydrochloride are well-known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology

No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)

As these products are intended for generic substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these products from a non-clinical perspective.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of vardenafil hydrochloride is well-known. With the exception of the bioequivalence studies detailed below, no new clinical studies have been performed and none are required for this type of applications. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

Study 1:

This is a single center, randomised, single dose, 4-period, 2-sequence replicate crossover comparative bioavailability study of the test product Vardenafil 20mg Tablets and Levitra 20mg film-coated Tablets (Bayer Pharma AG, Germany) in healthy, adult, human male subjects under fasting conditions.

After a fast of at least 10 hours, each subject received a single oral dose (1 x 20mg) of the test formulation or a single oral dose (1 x 20mg) of the reference formulation administered with 250 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days.

Results

Summary statistics for pharmacokinetic parameters for vardenafil for the test and reference product are shown below:

Parameter	R/R Intra-subject C.V (%)	T/R Intrasubject C.V (%)	Geometric LSMeans***		Ratio (%)	90% Confidence Limits (%)	
C_{max}	55.8	43.2	14132.0	12836.12	110.10	95.85	126.45
AUC_{0-T}	N/A	26.7	47190.4	45252.40	104.28	95.51	113.86

The bioequivalence study submitted by the applicant was performed according to the respective Note for Guidance and GCP requirements. The 90% confidence interval

(CI) for the geometric mean ratio of AUC_{0-T} was contained within 80-125%, but for C_{max} the interval was outside this range. However, the study was of a replicate design and a widened CI of 69.84 – 143.19% is proposed based on the within subject CV of 55.8% observed for the reference product. Review of the data does not create concern that the high variability is generated by outliers, and so the widened limits are considered to be acceptable. Therefore, bioequivalence between the test product (Vardenafil 20mg Film-coated Tablets) and reference product (Levitra 20mg Tablets) has been demonstrated.

As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study for the 20mg formulation e can be extrapolated to the 5 and 10mg strengths.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

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

IV.5 Clinical safety

No new safety data were submitted and none were required for this type of application.

IV.6 Risk Management Plan (RMP)

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 Vardenafil 5, 10 and 20mg 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
Hypersensitivity	- Contraindication in section 4.3 of the SmPC - Warning in section 2 of the PIL - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Decrease in blood pressure	- Contraindication in section 4.3 of the SmPC - Warning in section 4.4 of the SmPC - Undesirable effects in section 4.8 of the SmPC - Warning in section 2 of the PIL - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Effects on QT-interval and cardiac rhythm (arrhythmias)	- Warning in section 4.4 of the SmPC - Undesirable effects in section 4.8 of the SmPC - Study information in section 5.1 of the SmPC - Warning in section 2 of the PIL - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Prolonged erection, priapism	- Warning in section 4.4 of the SmPC - Undesirable effects in section 4.8 of the SmPC - Warning in section 2 of the PIL	No additional risk minimisation measures are currently proposed.
Interaction with CYP3A4 inhibitors (risk of overdose)	- Warning in section 4.2 of the SmPC - Contraindication in section 4.3 of the SmPC - Warning in section 4.4 of the SmPC - Interaction warning in section 4.5 of the SmPC - Warning in section 2 of the PIL	No additional risk minimisation measures are currently proposed.
Interaction with alpha-blockers (risk of hypotension)	- Warning in section 4.4 of the SmPC - Interaction warning in section 4.5 of the SmPC - Warning in section 2 of the PIL	No additional risk minimisation measures are currently proposed.
Interaction with nitrates or NO donors (risk of hypotension)	- Contraindication in section 4.3 of the SmPC - Interaction warning in section	No additional risk minimisation measures are currently proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.5 of the SmPC - Warning in section 2 of the PIL	
Interaction with riociguat (risk of hypotension)	- Contraindication in section 4.3 of the SmPC - Interaction warning in section 4.5 of the SmPC - Warning in section 2 of the PIL	No additional risk minimisation measures are currently proposed.
Counterfeit drug product	- Description in section 3 of the SmPC - Description in section 6.5 of the SmPC - Description in section 6 of the PIL	No additional risk minimisation measures are currently proposed.
Access to drug product without prescription	- Description in section 3 of the SmPC - Description in section 6.5 of the SmPC - Warning in opening paragraphs of PIL - Warning in section 2 of the PIL	No additional risk minimisation measures are currently proposed.

Important Potential Risks

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
NAION (Non-Arteritic Ischaemic Optic Neuropathy), transient and permanent vision loss	- Contraindication in section 4.3 of the SmPC - Warning in section 4.4 of the SmPC - Caution in section 4.7 of the SmPC - Undesirable effects in section 4.8 of the SmPC - Warning in section 2 of the PIL - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Transient global amnesia	- Undesirable effects in section 4.8 of the SmPC - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Epilepsy/seizure/convulsion	- Undesirable effects in section 4.8 of the SmPC - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.
Central Serious Retinopathy	- Warning in section 4.4 of the SmPC - Caution in section 4.7 of the	No additional risk minimisation measures are currently proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC - Undesirable effects in section 4.8 of the SmPC - Warning in section 2 of the PIL - Side effects in section 4 of the PIL	
Sudden deafness	- Undesirable effects in section 4.8 of the SmPC - Side effects in section 4 of the PIL	No additional risk minimisation measures are currently proposed.

Missing information

None

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

IV.7 Discussion on the clinical aspects

There are no objections to the approval of these products from a clinical perspective.

V User consultation

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Vardenafil Holsten 5 mg, 10 mg and 20 mg Tablets. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

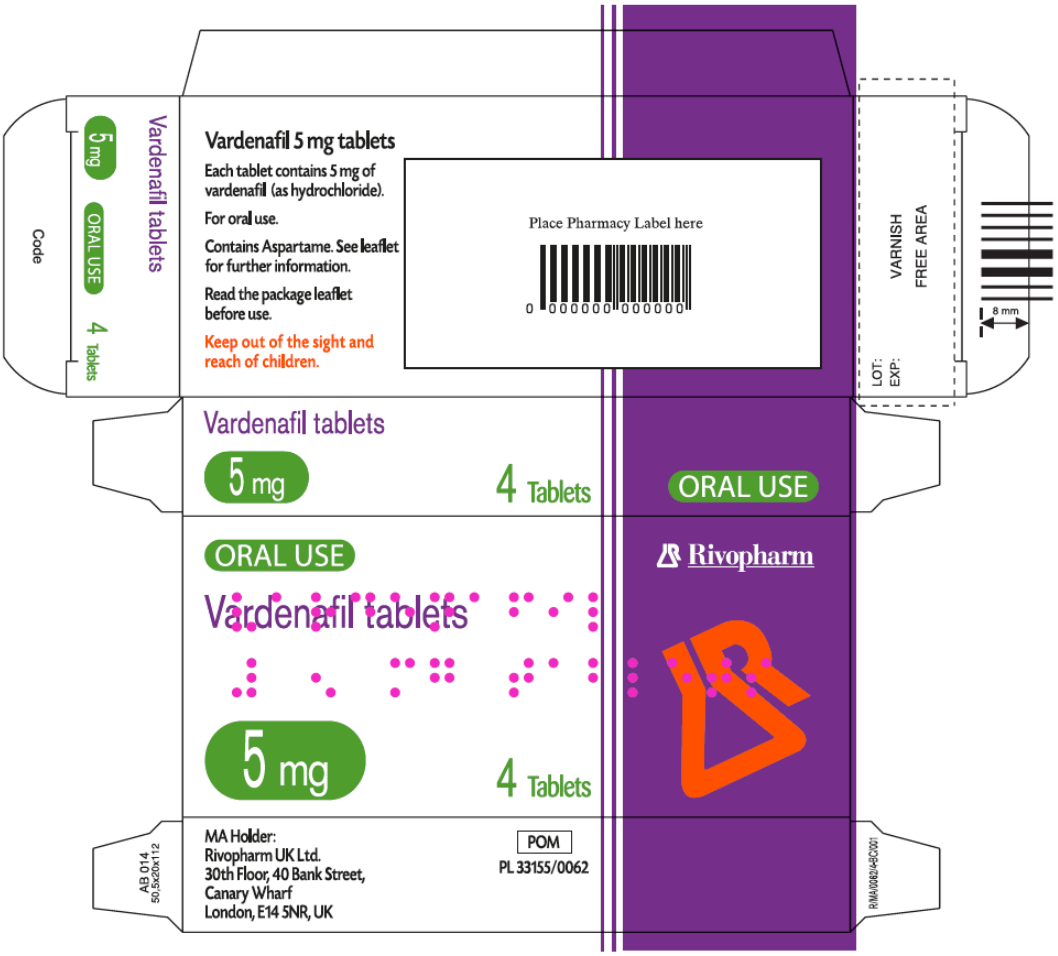
VI Overall conclusion, benefit/risk assessment and recommendation

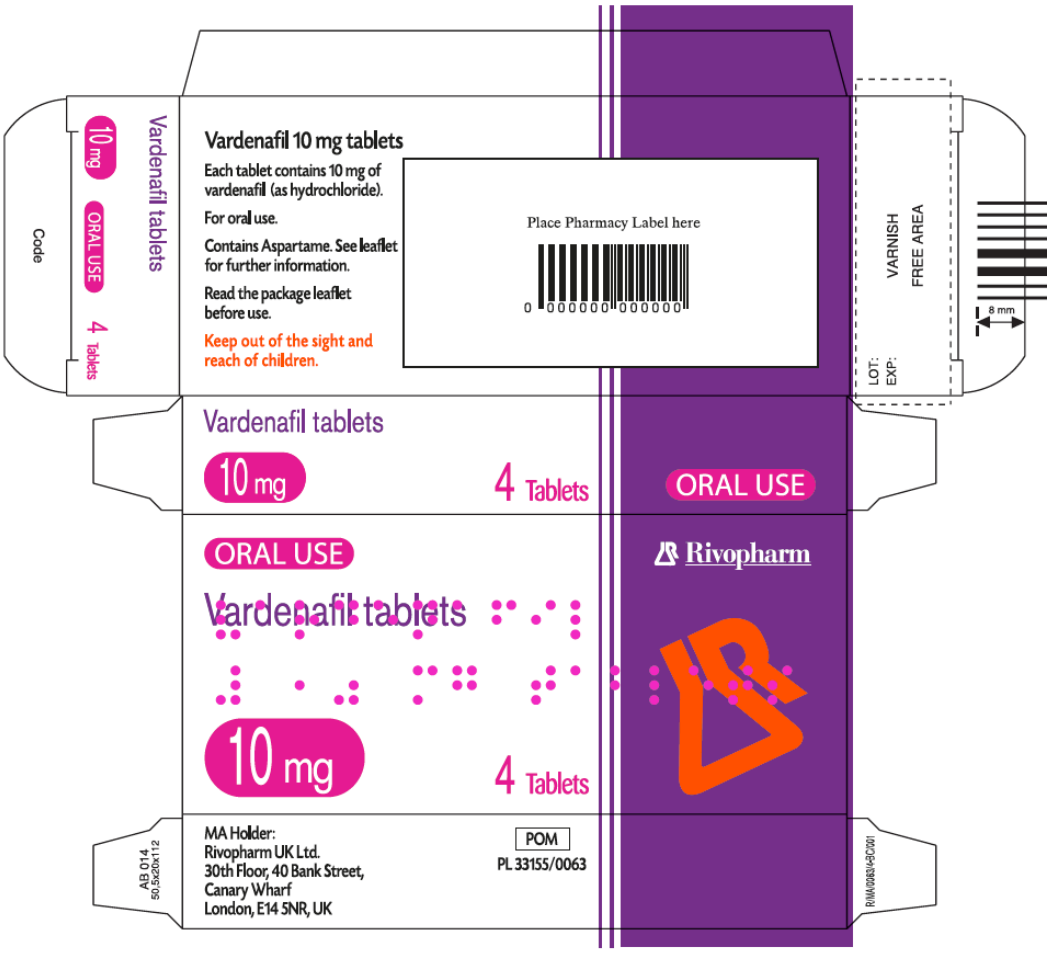
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with vardenafil hydrochloride is considered to have demonstrated the therapeutic value of the compound. The products are considered to be bioequivalent to the marketed reference products and their benefits and risks are considered similar. The benefit-risk balance is, therefore, considered to be positive.

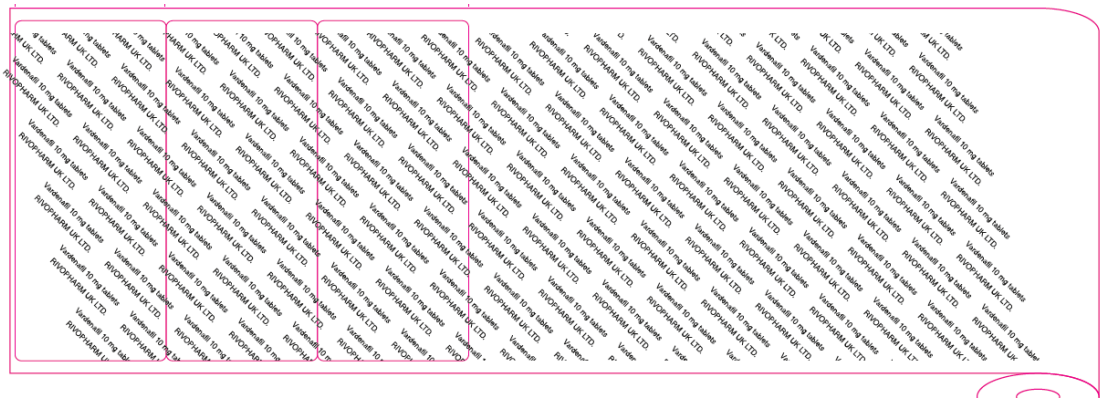
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

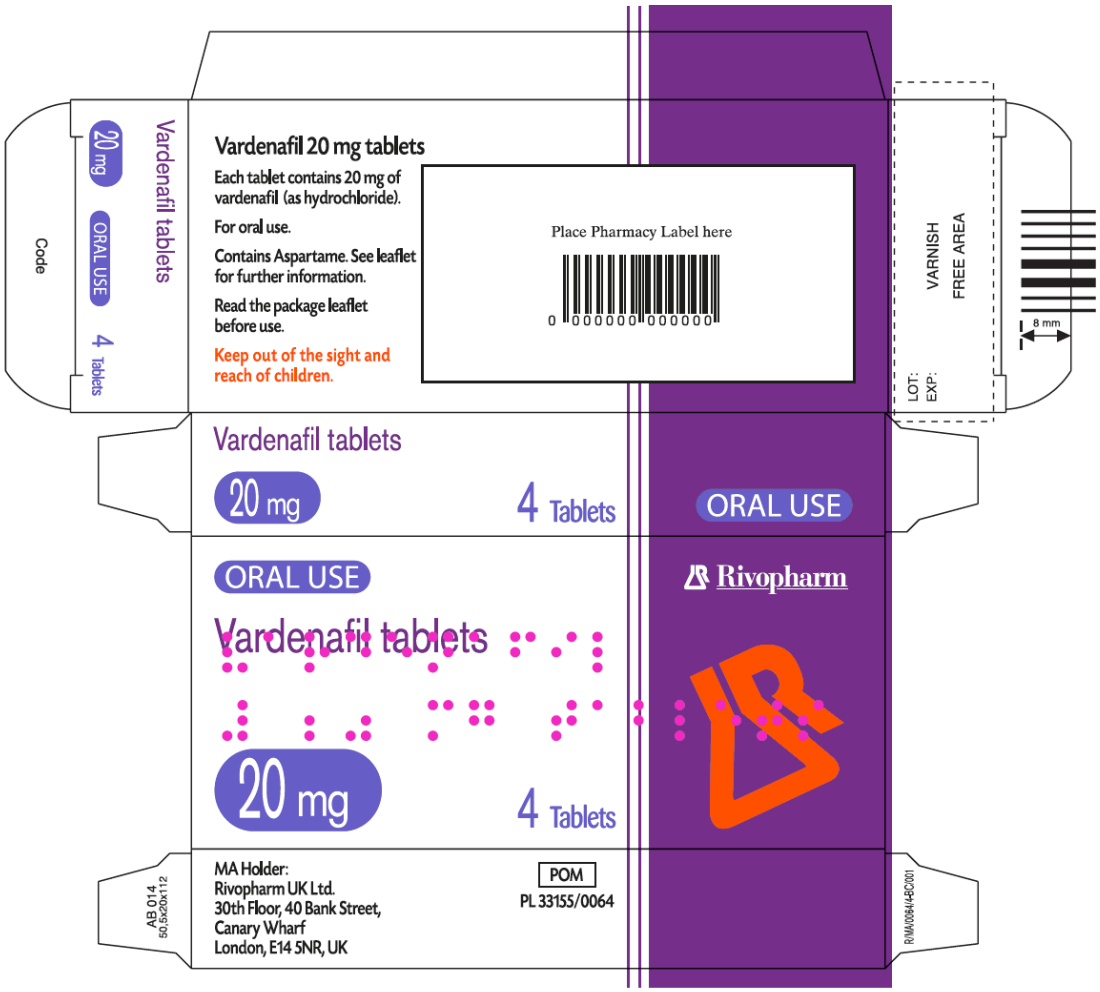
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Vardenafil 5, 10 and 20mg tablets is presented below:




Vardenafil 10 mg tablets
Each tablet contains 10 mg of vardenafil (as hydrochloride).
For oral use.
Contains Aspartame. See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Place Pharmacy Label here
VARNISH FREE AREA
LOT:
EXP:
8 mm
Code
10 mg
ORAL USE
4 Tablets
Vardenafil tablets
Vardenafil tablets
10 mg
4 Tablets
ORAL USE
ORAL USE
Vardenafil tablets
10 mg
4 Tablets
Rivopharm
MA Holder:
Rivopharm UK Ltd.
30th Floor, 40 Bank Street,
Canary Wharf
London, E14 5NR, UK
POM
PL 33155/0063
AB 014
50.5x20x112
RIVA/0082/04/PC001




Vardenafil 20 mg tablets
Each tablet contains 20 mg of vardenafil (as hydrochloride).
For oral use.
Contains Aspartame. See leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Place Pharmacy Label here
VARNISH FREE AREA
LOT:
EXP:
8 mm
Code
20 mg
ORAL USE
4 Tablets
Vardenafil tablets
Vardenafil tablets
20 mg
4 Tablets
ORAL USE
ORAL USE
Vardenafil tablets
20 mg
4 Tablets
Rivopharm
MA Holder:
Rivopharm UK Ltd.
30th Floor, 40 Bank Street,
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London, E14 5NR, UK
POM
PL 33155/0064
AB 014
50,5x20x112
RIVM/0064/HPC/001

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)