IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Vardenafil 5 mg film-coated tablets
VARDENAFIL HYDROCHLORIDE TRIHYDRATE
PA2315/073/001

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 Vardenafil 5 mg, 10 mg and 20 mg Film-coated Tablets from Accord Healthcare Ireland Ltd for the treatment of erectile dysfunction in adult men.

The legal basis for the application was article 10(1) i.e. this was a generic application. The reference product used for the bioequivalence study submitted in support of the application was Levitra 20mg Film coated tablets.

This product will be available on prescription only.

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

Name of the product	Vardenafil
Name(s) of the active substance(s) (INN)	VARDENAFIL HYDROCHLORIDE TRIHYDRATE,VARDENAFIL HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	G04BE09
Pharmaceutical form and strength(s)	5mg, 10mg, 20mg
Marketing Authorisation Number(s) in Ireland (PA)	PA2315/073/001-003
Marketing Authorisation Holder	Accord Healthcare Ireland Ltd

II. QUALITY ASPECTS

II.1. Introduction
This application is for Vardenafil 5/10 & 20 mg film coated tablets

II.2 Drug substance
The active substance is Vardenafil hydrochloride trihydrate 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)
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 the dosage form, 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.

Adventitious Agent Safety
N/A

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 Vardenafil 5 mg, 10 mg and 20 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This active substance is a generic formulation of Levitra on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment
An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.6 Discussion on the non-clinical aspects
Pharmacodynamic, pharmacokinetic and toxicological properties of Vardenafil are well known. As Vardenafil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical sections of the SmPC are in line with that of the reference product.

IV. CLINICAL ASPECTS

Vardenafil hydrochloride Trihydrate is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Levitra 20mg EU/1/03/248/009-01 marketed by Bayer Pharma AG.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Vardenafil 5mg,10mg and 20mg Film-coated Tablets is compared with the pharmacokinetic profile of the reference product Levitra 20mg EU/1/03/248/009-01 marketed by Bayer Pharma AG.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out.
Based on the pharmacokinetic parameters of active substance Vardenafil Accord and the reference tablet Levitra 20mg EU/1/03/248/009-01 marketed by Bayer Pharma AG are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

For multiple strengths, a comment on dose proportionality may be required, as follows:
The 5-20mg strengths and pharmaceutical form are dose proportional.

The data obtained from the bioequivalence study with the 20mg strength can be extrapolated to the other dosage strengths, based on the following criteria:

1] the pharmaceutical products are manufactured by the same manufacturer and process;
2] the input of both drugs is linear over the therapeutic dose range;
3] the qualitative composition of the different strengths is the same;
4] the ratio between amounts of active substance and excipients is similar, and
5] the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

- *Risk Management Plan (usual pharmacovigilance requirements and/or additional requirements)*
- *The proposed schedule for submission of PSURs should be addressed.*

The content of the SmPC approved during the national/MR/decentralised procedure is in accordance with that accepted for the reference product Levitra Film-coated tablets marketed by Bayer Pharma AG .

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Healthy Subject PK
The pharmacokinetics of vardenafil are approximately dose proportional over the recommended dose range (Rxlist 2014).

Absorption
Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15%. Maximum observed plasma concentrations after a single 20 mg dose in healthy volunteers are usually reached between 30 minutes and 2 hours (median 60 minutes) after oral dosing in the fasted state. Two food-effect studies were conducted which showed that high-fat meals caused a reduction in Cmax by 18%-50% (Klotz et al. 2001,
Rxlist 2014).

Distribution
The mean steady-state volume of distribution (Vss) for vardenafil is 208 L, indicating extensive tissue distribution. Vardenafil and its major circulating metabolite, M1, are highly bound to plasma proteins (about 95% for parent drug and M1) This protein binding is reversible and independent of total drug concentrations (Klotz et al. 2001, Rxlist 2014). Following a single oral dose of 20 mg vardenafil in healthy volunteers, a mean of 0.00018% of the administered dose was obtained in semen 1.5 hours after dosing (Klotz et al. 2001, Rxlist 2014).

Metabolism
Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. M1 is subject to further metabolism. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar
to that of vardenafil and an in vitro inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity (Klotz et al. 2001, Rxlist 2014).

Excretion
The total body clearance of vardenafil is 56 L/h, and the terminal half-life of vardenafil and its primary metabolite (M1) is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose) (Klotz et al. 2001, Rxlist 2014).

Patient PK
Hepatic Impairment In volunteers with mild hepatic impairment (Child-Pugh A), the C max and AUC following a 10 mg vardenafil dose were increased by 22% and 17%, respectively, compared to healthy control subjects. In volunteers with moderate hepatic impairment (Child-Pugh B), the C max and AUC following a 10 mg vardenafil dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment (Rxlist 2014).

Renal Impairment
In male volunteers with CLcr = 50–80 mL/min, the pharmacokinetics of vardenafil were similar to those observed in a control group with CLcr > 80 mL/min. In male volunteers with CLcr = 30–50 mL/min or CL cr < 30 mL/min renal impairment groups, the AUC of vardenafil was 20–30% higher compared to that observed in a control group with CLcr > 80 mL/min). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis (Rxlist 2014).

Intrinsic factor PK
Geriatric
In a healthy volunteer study of elderly males (≥ 65 years) and younger males (18–45 years), mean Cmax and AUC were 34% and 52% higher, respectively, in the elderly males (Rxlist 2014).
Extrinsic factor PK
Food
Two food-effect studies were conducted which showed that high-fat meals caused a reduction in Cmax by 18%-50% (Rajagopalan et al. 2003, Bischoff 2004, Rxlist 2014

IV.3 Pharmacodynamics
Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC code: G04BE09. Vardenafil is an oral therapy for the improvement of erectile function in men with erectile dysfunction. In the natural setting, i.e., with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

Penile erection is a haemodynamic process. During sexual stimulation, nitric oxide is released. It activates the enzyme guanylate cyclase, resulting in an increased level of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. This in turn results in smooth muscle relaxation, allowing increased inflow of blood into the penis. The level of cGMP is regulated by the rate of synthesis via guanylate cyclase and by the rate of degradation via cGMP hydrolysing phosphodiesterases (PDEs).

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.

In vitro studies have shown that vardenafil is more potent on PDE5 than on other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, PDE3, PDE4, PDE7, PDE8, PDE9 and PDE10).

In a penile plesthysmography (RigiScan) study, vardenafil 20 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 15 minutes after dosing. The overall response of these subjects to vardenafil became statistically significant, compared to placebo, 25 minutes after dosing.

Vardenafil causes mild and transient decreases in blood pressure which, in the majority of the cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 20 mg and 40 mg vardenafil were – 6.9 mmHg under 20 mg and – 4.3 mmHg under 40 mg of vardenafil, when compared to placebo. These effects are consistent with the vasodilatory effects of PDE5-inhibitors and are probably due to increased cGMP levels in vascular smooth muscle cells. Single and multiple oral doses of vardenafil up to 40 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

A single dose, double blind, crossover, randomised trial in 59 healthy males compared the effects on the QT interval of vardenafil (10 mg and 80 mg), sildenafil (50 mg and 400 mg) and placebo. Moxifloxacin (400 mg) was included as an active internal control. Effects on the QT interval were measured one hour post-dose (average tmax for vardenafil). The primary objective of this study was to rule out a greater than 10 msec effect (i.e., to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval compared to placebo, as measured by the change in Fridericia's correction formula (QTcF = QT/RR1/3) from baseline at the 1 hour post-dose time point. The vardenafil results showed an increase in QTc (Fridericia) of 8 msec (90% CI: 6-9) and 10 msec (90% CI: 8-11) at 10 and 80 mg doses compared to placebo and an increase in QTci of 4 msec (90% CI: 3-6) and 6 msec (90% CI: 4-7) at 10 and 80 mg doses compared to placebo, at one hour post-dose. At tmax, only the mean change in QTcF for vardenafil 80 mg was out of the study established limit (mean 10 msec, 90% CI: 8-11). When using the individual correction formulae, none of the values were out of the limit.

In a separate post-marketing study of 44 healthy volunteers, single doses of 10 mg vardenafil or 50 mg sildenafil were co-administered concomitantly with 400 mg gatifloxacin, a drug with comparable QT effect. Both vardenafil and sildenafil

showed an increase of Fridericia QTc effect of 4 msec (vardenafil) and 5 msec (sildenafil) when compared to either drug alone. The actual clinical impact of these QT changes is unknown.

Further information on clinical trials with vardenafil 10 mg orodispersible tablets
Efficacy and safety of vardenafil 10 mg orodispersible tablets were separately demonstrated in a broad population in two studies including 701 randomized erectile dysfunction patients who were treated up to 12 weeks. The distribution of patients in the predefined subgroups was covering elderly patients (51%), patients with history of diabetes mellitus (29%), dyslipidemia (39%) and hypertension (40%).

In pooled data from the two vardenafil 10 mg orodispersible tablets trials, IIEF-EF domain scores were significantly higher with vardenafil 10 mg orodispersible tablet versus placebo.

A percentage of 71% of all sexual attempts reported in the clinical trials had successful penetration compared to 44% of all attempts in the placebo group. These results were also reflected in subgroups, in elderly patients (65%), in patients with history of diabetes mellitus (63%), patients with history of dyslipidemia (66%) and hypertension (70%) of all sexual attempts reported had successful penetration.

About 63% of all reported sexual attempts with vardenafil 10 mg orodispersible tablets were successful in terms of erection maintenance compared to about 26% of all placebo-controlled sexualattempts. In the predefined subgroups 57% (elderly patients), 56% (patients with history of diabetes mellitus), 59% (patients with history of dyslipidemia) and 60% (patients with history of hypertension) of all reported attempts with vardenafil 10 mg orodispersible tablets were successful in terms of maintenance of erection.

Further information on clinical trials
In clinical trials vardenafil was administered to over 17,000 men with erectile dysfunction (ED) aged 18-89 years, many of whom had multiple co-morbid conditions. Over 2,500 patients have been treated with vardenafil for six months or longer. Of these, 900 patients have been treated for one year or longer.

The following patient groups were represented: elderly (22%), patients with hypertension (35%), diabetes mellitus (29%), ischaemic heart disease and other cardiovascular diseases (7%), chronic pulmonary disease (5%), hyperlipidemia (22%), depression (5%), radical prostatectomy (9%). The following groups were not well represented in clinical trials: elderly (>75 years, 2.4%), and patients with certain cardiovascular conditions (see section 4.3). No clinical trials in CNS diseases (except spinal cord injury), patients with severe renal or hepatic impairment, pelvic surgery (except nerve- sparing prostatectomy) or trauma or radiotherapy and hypoactive sexual desire or penile anatomic deformities have been performed.

Across the pivotal trials, treatment with vardenafil (film-coated tablets) resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo.

In fixed dose studies (film-coated tablets) in a broad population of men with erectile dysfunction, 68% (5 mg), 76% (10 mg) and 80% (20 mg) of patients experienced successful penetrations (SEP 2) compared to 49% on placebo over a three month study period. The ability to maintain the erection (SEP 3) in this broad ED population was given as 53% (5 mg), 63% (10 mg) and 65% (20 mg) compared to 29% on placebo.

In pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%).

In a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 61% and 49% on 10 mg and 64% and 54% on 20 mg vardenafil compared to 36% and 23% on placebo for patients who completed three months treatment.

In a clinical trial in post-prostatectomy patients, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10 mg and 20 mg. The response rates for the ability to obtain and maintain an erection was 47% and 37%

on 10 mg and 48% and 34% on 20 mg vardenafil compared to 22% and 10% on placebo for patients who completed three months treatment.

In a flexible-dose clinical trial in patients with Spinal Cord Injury, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo. The number of patients who returned to a normal IIEF domain score (≥ 26) were 53% on vardenafil compared to 9% on placebo. The response rates for the ability to obtain and maintain an erection were 76% and 59% on vardenafil compared to 41% and 22% on placebo for patients who completed three months treatment which were clinically and statistically significant ($p<0.001$).
The safety and efficacy of vardenafil was maintained in long-term studies.

IV.4 Clinical Efficacy
The efficacy of vardenafil was evaluated in several double-blind, randomized, placebocontrolled, multicenter trials in thousands of men with a wide age distribution and of
different races as well as different etiology of erectile dysfunction.A description of clinical trails using vardenafil for the proposed indication is given above.

In this registration file a vardenafil immediate release formulation is described and a bioequivalence study is presented to show therapeutic equivalence to the innovator product i.e.

'*An open labelled, randomized, single dose, two way crossover bioequivalence study of Vardenafil 20mg Film coated tablets in healthy human, adult male subjects under fasting conditions.*'

IV.5 Clinical Safety
The adverse reactions reported with Vardenafil in clinical trials were generally transient and mild to moderate in nature. The most commonly reported adverse drug reaction occurring in ≥ 10% of patients is headache. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. However, there are
several issues that have to be consider before prescribing Vardenafil, e.g., its effects on the cardiovascular system, on the eyes and on hearing as well as its potential for drug interactions.

It is concluded that vardenafil is an efficacious drug, however careful use is advised due to potential side effects and drug interactions.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

The schedule for Periodic Safety Update Reports (PSUR) submission should be addressed

Risk Management Plan

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 Vardenafil 5mg, 10mg & 20mg film coated tablets. The revised RMP (version 1 dated final sign off 25/06/2019) is acceptable.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity; • Hypotension or increased hypotensive effect; • Effects on QT interval and cardiac rhythm; • Prolonged erection, priapism;
Important potential risks	• NAION, transient & permanent vision loss; • Transient global amnesia; • Epilepsy/seizure/convulsion; • Central serious retinopathy; • Sudden deafness;

Missing information	• None;

Pharmacovigilance Plan
Routine pharmacovigilance has been proposed which is considered acceptable

Risk minimisation
Routine risk minimisation measures has been proposed which is considered acceptable.

Periodic Safety Update Report (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 Article10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date

Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects
N/A

V. OVERALL CONCLUSIONS

Vardenafil 20mg film coated tablets Accord Healthcare Ireland Ltd., is a generic form of Levitra 20mg film coated tablets of Bayer Pharma, Germany.
Levitra 20mg film coated tablets of Bayer Pharma, Germany is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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 Vardenafil 20mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The HPRA, on the basis of the data submitted considered that Vardenafil Film coated tablets was the same as the reference product and therefore granted a marketing authorisation.

VI. REVISION DATE