LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vardenafil Krka
(vardenafil)

SE/H/1619/01-03/DC

This module reflects the scientific discussion for the approval of Vardenafil Krka. The procedure was finalised on 2017-02-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Vardenafil Krka, 5 mg 10 mg, 20 mg, film coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, KRKA, d.d., Novo mesto applied through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DK, ES, FI, FR, IE, IT, NO, PT and UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Levitra, film-coated tablet authorised in MS since 2003, with Bayer Pharma AG as marketing authorisation holder.

The reference product used in the bioequivalence study is Levitra, 20 mg, film-coated tablet from DE with Bayer Pharma AG as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Vardenafil, 20 mg, film-coated tablet with Levitra, 20 mg, film-coated tablet under fasting conditions. The study was conducted at Pharma Medica Research Inc., Canada between 24th May and 1st June 2015. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of vardenafil were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.
From a pharmacokinetic point of view, absence of studies with the additional strengths 5 and 10 mg is acceptable, as the pharmacokinetics of vardenafil is linear between 5 mg and 20 mg.

Bioequivalence between the test and reference product has been adequately demonstrated.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted an updated risk management plan (RMP v1.1, dated 19 december 2016), 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 Krka, Viavardis and Vardegin.

Safety specification

Summary table of safety concerns as approved.

Important identified risks	Hypersensitivity
	Hypotension/Increased hypotensive effect (especially in combination with alpha-blockers, nitrates or NO-donors
	Effects on QT-interval and cardiac rhythm
	Prolonged erection
	Interaction with CYP3A4 inhibitors
Important potential risks	Ocular adverse events: NAION
	Transient amnesia
	Epilepsy/Seizure/Convulsion
	Central serous retinopathy
	Sudden deafness
Missing information	*Not applicable.*

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity	(Proposed) content in SPC: - contraindication is included in section 4.3 Prescription only medicine	None proposed.
Hypotension/Increased hypotensive effect (especially in combination with alpha-blockers, nitrates or NO-donors	(Proposed) content in SPC: - contraindication is included in section 4.3 - warning and precautions for use in section 4.4 - information on drug interactions is provided in	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	section 4.5 - listed in section 4.8 - information is included in section 5.1 Prescription only medicine	
Effects on QT-interval and cardiac rhythm	(Proposed) content in SPC: - warning and precautions for use in section 4.4 - listed in section 4.8 - information is included in section 5.1 Prescription only medicine	None proposed.
Prolonged erection	(Proposed) content in SPC: - warning and precautions for use in section 4.4 - listed in section 4.8 - information is included in section 5.1 Prescription only medicine	None proposed.
Interaction with CYP3A4 inhibitors	(Proposed) content in SPC: - warning in section 4.2 - contraindication is included in section 4.3 - warning and precautions for use in section 4.4 - information on drug interactions is provided in section 4.5 - information is included in section 5.2 Prescription only medicine	None proposed.
Important potential risks		
Ocular adverse events: NAION	(Proposed) content in SPC: - contraindication is included in section 4.3 - warning and precautions for use in section 4.4 - warning on the ability to drive in section 4.7 - listed in section 4.8 Prescription only medicine	None proposed.
Transient amnesia	(Proposed) content in SPC: - listed in section 4.8 Prescription only medicine	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Epilepsy/Seizure/Convulsion	(Proposed) content in SPC: - listed in section 4.8 Prescription only medicine	None proposed.
Central serous retinopathy	(Proposed) content in SPC: - warning on the ability to drive in section 4.7 - listed in section 4.8 Prescription only medicine	None proposed.
Sudden deafness	(Proposed) content in SPC: - listed in section 4.8 Prescription only medicine	None proposed.
Missing information		
Not applicable.		

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.
update of a RMP coincide, they can be submitted at the same time, but via different procedures

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Vizarsin 25, 50 and 100 mg tablets containing the active substance sildenafil. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Vardenafil Krka, is found adequate. There are no objections to approval of Vardenafil Krka, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Vardenafil Krka, 5 mg 10 mg, 20 mg, film coated tablet was positively finalised on 2017-02-16.

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MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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