IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Sildenvia 50 mg film-coated tablets
Sildenafil citrate
PA2315/261/001

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 Sildenvia 50 mg film-coated tablet, from Accord Healthcare Ireland Limited on 5th January 2024 for use *in 'adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sidenvia to be effective, sexual stimulation is required*'.

This application for a marketing authorisation for Sildenvia 50mg film-coated tablets was submitted in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a 'hybrid' application.

Ireland acted as Reference Member state in this decentralised procedure (DCP).

The prescription status of Sildenvia 50mg film-coated tablet in Ireland is for supply as a non-prescription medicine in pharmacies only, following a detailed consultation with the pharmacist to ensure patient suitability.

The Applicant received regulatory/scientific advice in advance of this DCP procedure.

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	Sildenvia 50 mg film-coated tablet
Name(s) of the active substance(s) (INN)	Sildenafil citrate
Pharmacotherapeutic classification (ATC code)	G04BE03
Pharmaceutical form and strength(s)	50 mg film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA2315/261/001
Marketing Authorisation Holder	Accord Healthcare Ireland Limited
MRP/DCP No.	IE/H/1220/001/DC
Reference Member State	IE
Concerned Member State	

II. QUALITY ASPECTS

II.1. Introduction

This application is for Sildenvia 50 mg film-coated tablet.

II.2 Drug substance

The active substance is sildenafil citrate, 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

Each film-coated table contains sildenafil citrate equivalent to 50 mg of sildenafil.

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 film-coated 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 Sildenvia 50 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance, sildenafil citrate, is a generic formulation of Viagra 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

Since Sildenafil Tablets 50 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil are well understood. As sildenafil is a well-known active substance, the applicant has not provided additional studies and further studies are not required. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

This application for a marketing authorisation for Sildenvia 50mg film-coated tablets was submitted in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a 'hybrid' application.

Ireland acted as Reference Member state in this decentralised procedure (DCP).

The prescription status of Sildenvia 50mg film-coated tablet in Ireland is for supply as a non-prescription medicine in pharmacies only, following a detailed consultation with the pharmacist to ensure patient suitability.

Therefore, the Applicant has provided a separate detailed justification to support the non-prescription legal status of Sildenvia 50mg film-coated tablets, as part of this procedure.
The active substance sildenafil is currently approved for non-prescription use in the RMS, for the 50mg strength of sildenafil provided that a detailed consultation between the pharmacist and patient takes place to ensure safe patient selection for treatment.
The benefits and risks associated with the availability of sildenafil as a non-prescription medicine, including a discussion of the criteria for changing the legal classification as set out in the Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use, was specifically provided in this application, in addition to the Clinical Overview.

Sildenvia 50mg tablets are to be used in a similar way to the EU approved prescription only medicine (POM) Viagra 50 mg film-coated tablets and contain the same amount of sildenafil citrate, having the same indication and posology. The product information has been adapted to reflect the non-prescription supply status of Sildenvia 50mg film-coated tablets. This is in line with other 50mg sildenafil medicines which are approved for non-prescription supply in the RMS and in other EU MS.

In this context, the content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Viagra, with further amendments to the product information to reflect the non-prescription status in Ireland in line with authorised sildenafil 50mg tablets for non-prescription treatment of erectile dysfunction in men. Pharmacy supply of non-prescription Sildenvia 50mg film-coated tablet in Ireland will only occur following a detailed consultation with the pharmacist to ensure patient suitability/safe patient selection. Educational materials for pharmacy will be implemented as additional risk minimisation measures to support safe supply for treatment with sildenafil 50mg film-coated tablets in the pharmacy setting.

For this application, the applicant has submitted one bioequivalence study by way of supportive data (ref: procedure NL/H/1823/001-003/DC).

In this study, the pharmacokinetic profile of the test product Sildenafil citrate Tablets 100 mg was compared to that of the reference product (i.e. Viagra® (Sildenafil Citrate Tablets 100 mg) manufactured by Pfizer PGM France.

The choice of the reference product in the bioequivalence study was justified as the reference product has been registered through a centralised procedure. It is noted that this BE study was performed originally to support the approval of the POM Sildenafil Accord product and is therefore considered as supportive data in the context of this application for an OTC authorisation of the 50mg strength of the same Sildenafil product, as biowaiver approach was agreed to support the other strengths of Sildenafil, including the 50mg strength.
The requirements for biowaiver were met according to the EMA guideline on the investigation of bioequivalence.

Based on the pharmacokinetic parameters of active substance sildenafil citrate, the reference tablet Viagra® (Sildenafil Citrate Tablets 100 mg) manufactured by Pfizer PGM France and test tablet Sildenafil citrate Tablets 100 mg were bioequivalent with respect to the rate and extent of absorption and fulfilled the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. A biowaiver approach to support the 50mg strength was satisfactorily justified also.

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

IV.2 Pharmacokinetics
In addition to the bioequivalence study provided within the application as supportive data, the applicant has also provided a clinical overview outlining the pharmacokinetics of sildenafil based on literature; this is considered acceptable.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented with this application.
The applicant has provided a clinical overview outlining the pharmacodynamics based on literature; this is considered acceptable.

IV.4 Clinical Efficacy

The clinical efficacy of sildenafil in the indication for the treatment of erectile dysfunction in men is established in clinical use. No new clinical efficacy studies were provided and none are required.

For this hybrid application, the applicant has provided a detailed clinical overview which discusses the clinical efficacy of sildenafil which is based on literature; this is considered acceptable.

As supporting data, a bioequivalence study has also been submitted by the applicant which was previously assessed (ref: procedure NL/H/1823/001-003/DC).
This study was for the 100mg strength of Sildenafil Accord (POM) and a biowaiver approach was used for the 50mg strength in line with the Note for guidance on Bioavailability and
bioequivalence-CPMP/EQP/QWP/1401/98.
Sildenafil film-coated tablets were compared to the centrally authorised reference product Viagra film-coated tablets which are marketed by Upjohn EESV, as outlined above.

Essential similarity between the test and reference products was demonstrated.
Based on the pharmacokinetic parameters of active substance sildenafil, the reference
and test tablets were bioequivalent with extent to the rate and extent of absorption and fulfilled the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
The biowaiver approach was used for the lower strengths of sildenafil, in line with the Note for guidance on Bioavailability and Bioequivalence-CPMP/EQP/QWP/1401/98.

IV.5 Clinical Safety

The overall safety profile of sildenafil is well established and generally well known over many years of clinical use in the management of erectile dysfunction in men.
No additional clinical safety studies were provided which is acceptable for this application type.
The safety information in the SmPC and Package Leaflet are in line with those of the reference product and have been updated to reflect the non-prescription supply status of Sildenvia 50mg film-coated tablets, thus bridging to the approved product information for sildenafil 50mg tablets which are authorised for non-prescription use in Ireland and some EU member states.
No new safety concerns were identified during the Bioequivalence study which was previously assessed and submitted with this application, as supportive data.
The safety profile of sildenafil is well established and has been adequately discussed by the applicant.

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 Sildenvia 50 mg Film-coated tablet.

Summary table of safety concerns in approved RMP:

Important identified risks	• Symptomatic hypotension/increased hypotensive effect in men: taking nitrated or NO donors, including nitrites (e.g. amyl nitrate or 'poppers' for recreational use) who are not stabilized on alpha-blocker therapy

	• Penal tissue damage and/or permanent loss of potency due to priapism
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Sudden hearing loss • Symptomatic hypotension in men with pre-existing hypotension*
Missing information	• None

** Symptomatic hypotension is a decrease in blood pressure such that symptoms of hypotension such as dizziness, syncope of orthostatic hypotension are manifested.*

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Symptomatic hypotension/increased hypotensive effect in men: taking nitrated or NO donors, including nitrites (e.g. amyl nitrate or 'poppers' for recreational use) who are not stabilized on alpha-blocker therapy	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. • PIL sections 2 and 4 • Section 15 'instructions on use' of the labelling' • Information on this safety concern in relation to adjustment of dosage, monitoring signs and symptoms of symptomatic hypotension, and caution to be followed while using Sildenvia with the medicinal products containing nitrates/NO donor, including nitrites are mentioned in sections 4.2, 4.3, 4.4 and 4.5 of Sildenvia SmPC, section 2 of the PIL and section 15 of the labelling. **Additional risk minimisation measures:** • Essential information for pharmacists • Pharmacist checklist	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activity:** None
Penal tissue damage and/or permanent loss of potency due to priapism	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.8 • PIL section 2 and 4 • Section 15 'instructions on use' of the labelling. • Information on this safety concern in relation to monitoring symptom and risk factors is mentioned in	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire has been proposed for Penile tissue damage and/or permanent loss of potency due to priapism. **Additional pharmacovigilance activity:** None

	section 4.4 of Sildenvia SmPC, section 2 of the PIL and section 15 of the labelling. **Additional risk minimisation measures:** • Essential information for pharmacists • Pharmacist checklist	
Sudden hearing loss	**Routine risk minimisation measures:** • SmPC Section 4.8 • PIL section 4 **Additional risk minimisation measures:** • Essential information for pharmacists • Pharmacist checklist	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire has been proposed for sudden hearing loss **Additional pharmacovigilance activity:** None
NAION	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4 and 4.8 • PIL sections 2 and 4 • Section 15 'instructions on use' of the labelling • Information on this safety concern in relation to monitoring signs, symptoms associated with this safety concerns and stopping the treatment is mentioned in section 4.4 of Sildenvia SmPC, Section 2 of the PIL and section 15 of the labelling. **Additional risk minimisation measures:** • Essential information for Pharmacists • Pharmacist checklist	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire has been proposed NAION. **Additional pharmacovigilance activity:** None
Symptomatic hypotension in men with pre-existing hypotension	**Routine risk minimisation measures:** • SmPC section 4.3 • PIL section 2 • Section 15 'instructions on use' of the labelling	**Routine pharmacovigilance activity beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activity:** None

	• Information on this safety concern in relation to use of Sildenvia in pre-existing hypotensive patient is mentioned section 4.4 of Sildenvia SmPC, Section 2 of the PIL and section 15 of the labelling. **Additional risk minimisation measures:** • Essential information for pharmacists • Pharmacist checklist	

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 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

Sildenafil is a well-known active substance with established efficacy and tolerability over many years in the treatment of erectile dysfunction in men.

Sildenvia 50mg film-coated tablets is a generic form of Viagra which is a well-known medicinal product approved in Europe for the treatment of erectile dysfunction in men, which has a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.
In this context, the clinical pharmacology, efficacy and safety of the active substance are well known and have been adequately discussed in the clinical overview which is acceptable for this type of application.

The active substance sildenafil (50mg strength of sildenafil) is currently approved for non-prescription use in Ireland and in some other countries in Europe, following a detailed pharmacist consultation to ensure safe patient selection.

The prescription status of Sildenvia 50mg film-coated tablet in Ireland is for supply as a non-prescription medicine in pharmacies, following a detailed consultation with the pharmacist to ensure patient suitability. Educational materials for pharmacy will be implemented as additional risk minimisation measures to support safe supply for treatment with sildenafil 50mg film-coated tablets in the pharmacy setting.

In this context, the Applicant has provided a separate detailed justification to support the non-prescription status of Sildenvia 50mg film-coated tablets, as part of this procedure.
The benefits and risks associated with the availability of sildenafil as a non-prescription medicine, including a discussion of the criteria for changing the legal classification as set out in the Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use, was specifically provided in this application, in addition to the Clinical Overview.

Sildenvia 50mg tablets are to be used in a similar way to the EU approved prescription only medicine (POM) Viagra 50 mg film-coated tablets and contain the same amount of sildenafil citrate, having the same indication and posology. The product

information has been adapted to reflect the non-prescription supply status of Sildenvia 50mg film-coated tablets. This is in line with other 50mg sildenafil medicines which are approved for non-prescription supply in the RMS and in other EU MS and is acceptable.

In this context, the content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Viagra, with further amendments to the product information to reflect the non-prescription status in Ireland of sildenafil 50mg tablets for non-prescription treatment of erectile dysfunction in men.

For this application, the applicant has submitted one bioequivalence study by way of supportive data (ref: procedure NL/H/1823/001-003/DC).
Based on the pharmacokinetic parameters of active substance sildenafil citrate, the reference tablet Viagra 100mg tablets marketed by Upjohn EESV was shown to be bioequivalent to the test product Sildenafil 100mg tablets in healthy, adult subjects under fasting conditions with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
A biowaiver approach was used in relation to the lower strengths in line with the Note for guidance on Bioavailability-CPMP/EQP/QWP/1401/98, this approach is considered acceptable.

Overall, the efficacy and safety profile of the active substance sildenafil in the approved indication is well established over many years of use in the EU.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents (ref: procedure NL/H/1823/001-003/DC).

The SmPC is consistent with that of the reference product and has been bridged to reflect the SmPC wording for non-prescription supply status in Ireland.

A number of questions were raised during the assessment phase of the procedure and the applicant has provided satisfactory responses to all the points raised and has justified their
approach. This is considered acceptable.

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

Routine pharmacovigilance activities are proposed to continue to monitor and further characterise the safety concerns for the active substance. Additional risk minimisation measures in the form of educational materials for pharmacy will be implemented to support safe supply in the pharmacy setting.

The Applicant is requested to submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) 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.

V. OVERALL CONCLUSIONS

The active substance, sildenafil, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established efficacy and safety profile.
This decentralised application for a marketing authorisation for Sildenvia 50mg film-coated tablets was submitted to HPRA in accordance with Article 10.3 of Directive 2001/83/EC.

Sildenvia 50mg tablets are to be used in a similar way to the EU approved prescription only medicine (POM) Viagra 50 mg film-coated tablets which are marketed by Upjohn EESV, registered since 14/09/1998 and contain the same amount of sildenafil citrate, having the same indication and posology. The product information has been further adapted to reflect the non-prescription supply status of Sildenvia 50mg film-coated tablets. This is in line with other 50mg sildenafil medicines which are approved for non-prescription supply in Ireland and in other countries, including other EU member states where sildenafil can be supplied in a pharmacy setting following a detailed consultation between the patient and pharmacist to ensure that the patient is suitable for treatment in that setting.

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

Routine pharmacovigilance activities are proposed to continue to monitor and further characterise the safety concerns for the active substance. Additional risk minimisation measures in the form of educational materials for pharmacy will be implemented to support safe supply in the pharmacy setting.

The HPRA, on the basis of the data submitted considered that Sildenvia 50mg film-coated tablets demonstrated adequate evidence of efficacy and safety for the approved indication, as well as a satisfactory risk/benefit profile in line with that established in the EU and in Ireland for non-prescription supply of sildenafil and therefore granted a marketing authorisation.

VI. REVISION DATE

02.11.2028