IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Silesto 25 mg Chewable tablets
Sildenafil citrate
PA0126/388/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Clonmel Healthcare Ltd, Silesto 25 mg and 50 mg, Chewable tablets, on the 13th December 2024 for the treatment 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 Silesto (Sildenafil) to be effective, sexual stimulation is required.

This application for a marketing authorisation was submitted in accordance with Article 10.1 of Directive 2001/83/EC and is referred to as a "generic" application.

This means that the Marketing Authorisation Holder for Silesto 25 mg and 50 mg Chewable tablets, is issued based on the acceptable demonstration of bioequivalence to the designated reference product. The reference product is Viagra® 25/50/100 mg film-coated tablets from Upjohn EESV, France, registered centrally since 1998 (MA no. EU/1/98/077).

Ireland is the Reference Member State (RMS) in this decentralised procedure, Kappler Pharma Consult GmbH as the applicant has applied for Marketing Authorisations for Silesto 25 mg and 50 mg Chewable tablets in the Concerned Member States (CMS') Bulgaria and Romania.

This medicinal product is subject to prescription.

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	IE/H/1336/001-00/DC Silesto 25 mg and 50 mg Chewable tablets tablet
Name(s) of the active substance(s) (INN)	Sildenafil as Sildenafil Citrate
Pharmacotherapeutic classification (ATC code)	GO4BE03
Pharmaceutical form and strength(s)	Chewable tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0126/388/001-002
Marketing Authorisation Holder	Clonmel Healthcare Ltd
MRP/DCP No.	IE/H/1336/001-002/DC
Reference Member State	Ireland (IE)
Concerned Member State	Bulgaria (BG) & Romainia (RO)

II. QUALITY ASPECTS

This application is for Silesto 25 and 50 Chewable tablets.

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

The medicinal product contains 35.112 mg of Sildenafil citrate equivalent to 25 mg Sildenafil for the 25 mg strength, or 70.225 mg of Sildenafil citrate equivalent to 50 mg Sildenafil for the 50 mg strength and 140.48 mg of Sildenafil citrate equivalent to 100 mg Sildenafil for the 100 mg strength.

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 (chewable tablets) 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 tablets (chewable), 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 Silesto 25 and 50 mg Chewable tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Viagra film-coated tablets 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 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since the generic version of sildenafil 25mg, 50mg and 100 film-coated tablets listed above are not anticipated to increase the environmental exposure, additional environmental risk assessment studies are not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Sildenafil citrate are well known. As sildenafil citrate 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Viagra® 25/50/100 mg film-coated tablets marketed by Upjohn EESV.

For this generic application, the applicant has submitted a single bioequivalence study in which the pharmacokinetic profile of the test product Sildenafil 100 mg Chewable tablets as manufactured by Genepharm S.A., is compared with the pharmacokinetic profile of the reference product Viagra® 100 mg film-coated tablets

A single-dose, randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Sildenafil chewable tablets 100mg manufactured by Genepharm S.A., with VIAGRA ® 100 mg film-coated tablets of Pfizer Limited, UK, in normal, healthy, adult, male human subjects under fasting conditions was carried out in 2009.

Sildenafil Chewable tablets 100mg manufactured by Genepharm S.A was compared to the reference product VIAGRA ® 100 mg film-coated tablets of Pfizer Limited, UK. Based on the pharmacokinetic parameters of active substance sildenafil the reference tablet VIAGRA ® 100 mg film-coated tablets marketed by Upjohn EESV and test tablet sildenafil Chewable tablets 100mg are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for the 50mg and 25mg strengths was proposed. The biowaiver criteria were fulfilled as per Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/corr**). The results of the bioequivalence study performed with the Sildenafil 100 mg film coated tablets therefore apply to the other two strengths.

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

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IV.2 Pharmacokinetics

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41 % (range 25-63 %). After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100 mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in tmax of 60 minutes and a mean reduction in Cmax of 29 %.

Distribution
The mean steady state volume of distribution (Vd) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40 %). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96 % bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100 mg single dose), less than 0.0002 % (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Biotransformation
Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil.
This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50 % that of the parent drug. Plasma concentrations of this metabolite are approximately 40 % of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 h.

Elimination
The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

IV.3 Pharmacodynamics

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore, sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

IV.4 Clinical Efficacy

As appropriate, include brief description of specific studies including date and location, whether multicentre, blinded, controlled, inclusion criteria, number of patients, pivotal criteria/endpoints, degree of significance, outcome, conclusions.

IV.5 Clinical Safety

The efficacy of sildenafil in the proposed indications is established in clinical use. No additional efficacy clinical studies to demonstrate efficacy have been included in the application and none are required for a generic application.

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 the above-mentioned sildenafil containing products.

Safety specification

Important identified risks	• None
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION)/eye haemorrhage
Missing information	• None

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

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

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

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant has submitted the results of a suitable bioequivalence study with the 100 mg strength which has demonstrated the similarity of the test product against the reference product, in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/corr**). Justification for a biowaiver for the 25 mg and 50 mg strength was provided.

The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Silesto 25 mg and 50 mg Chewable tablets from applicant Kappler Pharma Consult GmbH is a generic form of Viagra 25 mg & 50 mg film-coated tablet by Upjohn EESV, Netherlands, registered centrally since 1998 (MA no. EU/1/98/077). Viagra® 25/50/100 mg film-coated tablets from Upjohn EESV, France, registered centrally since 1998 (MA no. EU/1/98/077) 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, Clonmel Healthcare Ltd 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 Silesto 25 mg and 50 mg Chewable tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

15th November 2029