December 2022

Public assessment summary report

Introduction

Name of the Finished Pharmaceutical Product	Sildenafil Citrate film coated tablets 50 mg
License holder of the finished product	Mega lifesciences limited. 384, Soi 6, Pattana 3 Road, Bangpoo Industrial Estate, Moo 4, Praeksa, Muang Samutprakarn, Samutprakarn 10280, Thailand
Manufacturer of the Finished Product	Macleods Pharmaceuticals Ltd. Block N-2, Village: Theda, PO: Lodhimajra, Tehsil Baddi, Dist: Solan, Himachal Pradesh – 174 101, India.
Active Pharmaceutical Ingredient(s) (API)	Sildenafil

Based on in depth review of quality, safety and efficacy data, the authority granted a marketing authorization for Sildenafil Citrate film coated tablets 50 mg, manufactured Macleods Pharmaceuticals Ltd, India. The active ingredient of Sildenafil Citrate film coated tablets is Sildenafil Citrate. Sildenafil is in a class of medications called Urologicals; Drugs used in erectile dysfunction.

ATC Code: G04B E03.

The product is indicated for:

Sildenafil Citrate is indicated 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 Sildenafil to be effective, sexual stimulation is required.

A compressive description of the indications and posology is given in the SmPC.

Assessment of quality

Active pharmaceutical Ingredient (API)

INN name: Sildenafil citrate

Chemical name: *Piperazine, 1 -[[3 -(6,7-dihydro-1-methyl-7-oxo-3-propyl- 1Hpyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-2- hydroxy-1, 2, 3-propanetricarboxylate (1:1)*
The active substance is a White to off white powder, Soluble in dimethylformamide, sparingly soluble in acetic acid, slightly soluble in methanol and water, practically insoluble in hexane at 25°C±02°C.

The proposed manufacturing process has been adequately described; critical steps and accompanying in-process controls have been defined to ensure quality of the final compound.

In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by various methods. Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.

The substance complies with the requirements of the Ethiopian medicine registration guideline for potential impurities.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. Testing methods are adequately drawn up and sufficiently validated. The reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised. Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability data have been obtained. The data show the substance to be stable. Based on the data submitted appropriate retest periods and storage conditions have been set.

GMP compliance of the API manufacture is demonstrated by document review.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture:

The aim of the pharmaceutical development was to develop Sildenafil Citrate 50 mg film coated tablets generic version to the reference innovator product. Tablets was developed in reference to Viagra® tablets containing 50 mg sildenafil as active substance, pharmaceutically equivalent and bioequivalent to the product Viagra® 50 mg (Sildenafil Tablets 50 mg) manufactured by Pfizer, UK.

A satisfactory package of data on development pharmaceutics has been presented. Brief

Discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final

Formulation is included in the documentation.

As a result of development studies product with the following composition, appearance and

Packaging was obtained. The used excipients were: Microcrystalline Cellulose RQ 101, Di basic, Calcium Phosphate Dihydrate , Croscarmellose sodium, Opadry Blue 03K80814 ,Magnesium stearate, Purified Water, Hypromellose (E-5 cps). All excipients used comply with their respective USP–NF/Ph. Eur monographs

Sildenafil Citrate 50 mg film coated tablets are Blue coloured, Diamond shaped, film coated tablets debossed with "CL 36" on one side and plain on the other side.

The film-coated tablets are packaged in Alu/PVC/PVdC Blister pack in a unit carton.

With regard to dissolution and impurity profile, the product is shown to be similar to the reference product. A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

Specifications:

The finished product specification is satisfactory. The acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of Ph.Eur.2.2.29 and acceptable in house standards. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for three productions are presented. Certificates of analysis were also provided for the working standard used.

The container closure system

For sildenafil citrate 50 mg film-coated tablets are packaged in Alu/PVC/PVdC Blister pack in a unit carton

Stability testing:

Same blisters as those proposed for routine storage were used for the stability studies.

Finished product stability studies have been conducted in accordance with the current medicine registration guideline of Ethiopia. Based on the results, a shelf-life of 36 months with storage conditions "*Store below 30°C in a dry place. Protect from moisture."* is considered acceptable for sildenafil citrate 50 mg strengths.

Assessment of bioequivalence

An open label, balanced, analyst blind, randomised, two-treatment, two-period , two-sequence, single dose, crossover bioequivalenc study of single dose Sildenafil Citrate Tablets 100 mg (each tablet contains sildenafil citrate equivalent to 100 mg sildenafil) manufactured by Macleods Pharmaceuticals Ltd ., India comparing with Viagra® 100 mg (sildenafil citrate) tablets (each tablet contains sildenafil citrate equivalent to 100 mg sildenafil) marketed by Pfizer Limited, United Kingdom was done on 48 healthy, adult, human male subjects under fasting condition at 90 % CI to show the bioequivalence of the test product with the reference product. Geometric means (AUC, Cmax) and arithmetic means (tmax) for Sildenafil Citrate as well as statistical results are summarised in the following tables:

Sildenafil Citrate Tablets 100 mg

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (geometric mean)	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
C_{max} (ng/mL)	681. 711	679.200	100.37	93.78 - 107.42
AUC_{0-t} (ng.h/mL)	2183.049	2266.577	96.31	92.14 -100.68
AUC_{0-inf} (ng.h/mL)	2257.915	2333.492	96.76	92.69 -101 .01

Based on the acceptance criteria (ln transformed value of Cmax and AUC0-t, 80-125) dose Sildenafil Citrate Tablets 100 mg Film-Coated Tablets manufactured by Macleods Pharmaceuticals Ltd, India is bioequivalent with Viagra® 100 mg (sildenafil citrate) tablets marketed by Pfizer Limited, United Kingdom.

Conclusion

Based on assessment of data on quality, bioequivalence, safety and efficacy the assessors considered that the benefit–risk profile of Sildenafil Citrate tablets 50 mg Film-Coated Tablets manufactured Macleods Pharmaceuticals Ltd, India was acceptable for the following indication(s): indicated 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 Sildenafil to be effective, sexual stimulation is required.

.