IPAR

Public Assessment Report

Scientific discussion

Blugral 25, 50 & 100mg Film-coated Tablets (Sildenafil Citrate)

IE/H/242/001-003/DC

This module reflects the scientific discussion for the approval of Blugral 25, 50 & 100mg Film-coated Tablets. The procedure was finalised on 26th November 2012. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

"Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for *Blugral, 25, 50 & 100mg Film-coated Tablets (sildenafil citrate*), from Niche Generics.

The product is indicated for*: erectile dysfunction.*
A comprehensive description of the indications and posology is given in the SmPC."

"The marketing authorisation has been granted pursuant to Article 10 (1) generic application of Directive 2001/83/EC."

Erectile dysfunction (**ED**) is sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual performance. Most cases are due to narrowing of the arteries supplying blood to the penis and the risk factors for erectile dysfunction are similar to those for coronary heart disease.

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.

No discussions were held with CMDh during the procedure.

II QUALITY ASPECTS

II.1 Introduction

Sildenafil 25mg, 50mg and 100mg film-coated tablets are diamond shaped, blue coloured, biconvex, film-coated tablets debossed with 'U' on one side and '25'/ '50'/ '100' on the other side respectively for the three strengths.

II.2 Drug Substance

The drug substance is sildenafil citrate, an established active substance of chemical origin. It is monographed in the European Pharmacopoeia.

The active substance specification includes relevant tests and the acceptance limits have been appropriately justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to support a the claimed retest period.

II.3 Medicinal Product

The development of the drug product formulation is well described. The qualitative composition is similar to that of the reference product, Viagra. Comparative *in vitro* dissolution profiles of the generic product and the reference product support the claim for similarity.
The excipients used in the product are all standard in the manufacture of tablets and are compliant with European Pharmacopoeia (or equivalent) requirements.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests and limits in the finished products specifications are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed for tablets in the commercial packaging; the data support the shelf life claimed in the SmPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The chemical and pharmaceutical aspects of the application are acceptable and there are no objections to the granting of the authorisation. There are no biological aspects to this application.

III NON-CLINICAL ASPECTS

III.1 Non-clinical overview

Pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil are well known. As sildenafil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is, thus, appropriate.

The non-clinical overview was written by appropriately qualified expert. It contains a review of 38 references published up to the year 2009 and covers all appropriate non clinical aspects. All relevant non-clinical findings have been described adequately in the corresponding sections of the product literature (SmPC).

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Blugral 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 non-clinical aspects of Blugral are expected to be similar to those of Viagra. There are no objections to the approval of Blugral from a non-clinical perspective

IV CLINICAL ASPECTS

IV.1 Introduction

A bioequivalence study performed in the fasting state demonstrated bioequivalence between 100mg of Blugral and 100mg of Viagra.

IV.2 Pharmacokinetics

In case of generic applications:

Biowaiver

A bioequivalence study for the highest strength (100 mg) was submitted. A biowaiver for the 25 mg and 50 mg strengths is appropriate. The pharmacokinetics are linear for the proposed dosing range (25 mg to 100 mg). All of the remaining criteria for a biowaiver have been met i.e: the products are manufactured by the same manufacturing process; the qualitive composition of the different strengths is the same; the composition of the different strengths are quantitatively proportional; and in vitro dissolution profiles are comparable.

Bioequivalence studies

One bioequivalence study in the fasted state **10-VIN-218** was submitted. The applicant states that the study was conducted under conditions of Good General Practice (GCP) and Good Laboratory Practice (GLP).

The study (10-VIN-218) was an open label, balanced, randomized, two-treatment, two-period two-sequence, single dose bioequivalence study conducted in healthy adult males under fasting conditions which compared Blugral 100mg (sildenafil citrate) to Viagra 100mg. The study was conducted under standardised conditions.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h
Test	**2788.179 ± 906.5790**	**2849.266 ± 932.7265**	**885.737 ± 325.8431**	**0.893 ± 0.5296**
Reference	**2778.292 ± 913.3381**	**2839.572 ± 946.6451**	**875.819 ± 324.3313**	**0.843 ± 0.6330**
***Ratio (90% CI)**	**100.62% (96.21%-105.23%)**	**100.67% (96.19% - 105.36%)**	**101.90% (94.05%-110.40%)**	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

*ln-transformed values

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Blugral is considered bioequivalent with Viagra

The results of study **10-VIN-218** with 100 mg formulation can be extrapolated to other strengths 25 mg and 50mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.3 Pharmacodynamics

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 caverosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8,9,10 and 11. In particular, sildenafil has greater then 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

IV.4 Clinical efficacy

The clinical efficacy of sildenafil is well characterised.

IV.5 Clinical safety

Viagra (sildenafil) was first authorised centrally in 1998. The clinical safety of sildenafil is well characterised.

IV.6 Discussion on the clinical aspects

This is an application for a generic version of a product which was first authorised in 1998. The submission of abridged applications for generic products avoids the need for repetitive tests on animals and humans.

Once bioequivalence has been demonstrated between the generic product and a reference product (in this case Viagra) it can be expected that the generic product and the reference product will have similar efficacy and safety. As bioequivalence has been demonstrated between Blugral 100mg and Viagra 100mg and conditions for a biowaiver for the 25mg and 50mg of Blugral have been met it can be assumed that Blugral is likely to have similar efficacy and safety to Viagra.

V OVERALL CONCLUSIONS

There were no discussions in CMDh, no specific obligations, nor any follow-up measures.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59 (3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI REVISION DATE

January 2013