CBG MEB

Public Assessment Report

Scientific discussion

Mifegyne 600 mg, tablets

(mifepristone)

NL/H/2937/001/DC

Date: 21 January 2015

This module reflects the scientific discussion for the approval of Mifegyne 600 mg, tablets. The procedure was finalised on 12 June 2014. 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 Mifegyne 600 mg, tablets from Exelgyn.

The product is indicated for:

- **Medical termination of developing intra-uterine pregnancy.**
  In sequential use with a prostaglandin analogue, up to 63 days of amenorrhea.
- **Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*.**
- **Labour induction in foetal death in utero.**
  In patients where prostaglandin or oxytocin cannot be used.

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

This decentralised procedure concerns a line extension of Mifegyne 200 mg tablets (NL/H/2937/002/DC). Mifegyne 200 mg is approved in the EU through an MRP, for which the Netherlands currently acts as RMS. In the Netherlands the marketing for this medicinal product was granted in 1999.

In addition to the indications listed above, a fourth indication is approved for the 200 mg strength: 'Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester'. This indication is however not applicable for the 600 mg strength.

It is expected that the 600 mg tablet will facilitate the use of the already approved 600 mg dose of mifepristone, which is currently administered as 3 tablets of 200 mg taken as a single oral dose, and will enable the prevention of incorrect use of mifepristone with a lower dose.

The concerned member states (CMS) involved in this procedure were France, Germany, Italy, Romania and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC, a full dossier application.

Since the application for Mifegyne 600 mg is a line extension of an already authorised product, the MAH did not submit new non-clinical and clinical studies, besides a bioequivalence study to compare the 600 mg tablet with 3 x 200 mg tablets. Reference is made to the non-clinical and clinical dossier of Mifegyne 200 mg. The MAH has updated the overviews of non-clinical and clinical data.

As Mifegyne 600 mg is part of the same Global Marketing Authorisation as the 200 mg authorisation, it is considered as 'already authorised'. Mifegyne has been developed and authorised before paediatric regulation EC 1901/2006 came into effect, and therefore a Paediatric Investigation Plan (PIP) is not required.

II. QUALITY ASPECTS

II.1 Introduction

Mifegyne 600 mg is a biconvex, light yellow, almond shaped tablet with a length of 19 mm and a width of 11 mm, with 'γ' engraved on one side and '600' on the other side.

The tablets are packed in PVC/aluminium blister packs.

The excipients are: colloidal anhydrous silica (E551), maize starch, povidone (E1201), magnesium stearate (E572), microcrystalline cellulose (E460).

II.2 Drug Substance

The active substance is mifepristone, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). It is a yellow crystalline powder which is very slightly soluble in water and slightly soluble in aqueous buffer solution pH 1. The route of synthesis of the active substance manufacturer results in one polymorphic form, Form I, exclusively.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis of mifepristone is described in 5 main steps. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The MAH applies the specifications of the active substance manufacturer with an additional specification for particle size distribution. The analytical methods are identical to those of the ASM. Data of three batches are provided in the dossier, demonstrating compliance with the specifications.

Stability of drug substance
Stability data on the active substance have been provided for six batches of non-micronized active substance stored at 25°C/60% RH (6-60 months) and 40°C/75% RH (6-12 months). No changes or trends were seen in any of het tested parameters. Furthermore, an additional stability study with two batches of micronized active substance was started at 25°C/60% RH (24 months data available) and 40°C/75% RH (6 months data available). The data showed no trends nor out of specification results.
The claimed retest period of 36 months without any special storage conditions is justified on the basis of the provided stability data.

II.3 Medicinal Product

Pharmaceutical development
Development of the 600 mg tablet was largely based on the development of the already authorized 200 mg tablet. It has been shown by dissolution criteria that the use of micronized active substance increases the dissolution rate and thus could have an influence on the *in vivo* absorption of this low solubility substance. The choice of the well known excipients is justified and their functions explained.
The formulation development has been adequately performed and described. A wet granulation manufacturing process has been selected because it is considered appropriate to give a consistently reliable performance for production of tablets with uniform active substance content when handling a micronized active substance.
The test Mifegyne 600 mg tablet and reference Mifegyne 200 mg tablet used in the bioequivalence study are dose-proportional formulations and bioequivalence was proven between 1 tablet of 600 mg and 3 tablets of 200 mg. Sufficient comparative *in-vitro* dissolution data have been provided. The bioequivalence study is approvable from a chemical-pharmaceutical perspective. In conclusion, the pharmaceutical development has been adequately performed.

Manufacturing process
The wet granulation process includes preparation of the moistening solution, mixing and moinstening/ lubrication. The manufacturing process of the final blend was already validated and authorised for the 200 mg tablets. As the manufacturing process is considered a standard process, it is acceptable that the process will be validated on the first three production batches post-approval.

Control of excipients

The excipients comply with Ph.Eur. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average mass, uniformity of dosage units, disintegration, dissolution test, identity, impurities, assay and microbial characteristics. The release and shelf-life limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two industrial-scale batches demonstrating compliance with the release specification. Post-approval a third production batch of the drug product will be tested for microbial quality to fully justify non-routine testing of microbial quality.

Stability of drug product
Stability data on the product has been provided for one batch that was stored at 30°C/75% RH (18 months) and 40°C/75% RH (6 months) and one batch that was stored at 25°C/60% RH (18 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC/Al blister. Besides the stability data on batches of the 600 mg product, supportive stability data have been provided on three production-scale batches of the 200 mg product. The stability data on the 600 mg tablets are in line with the supportive data on the already authorized 200 mg product. The stability data on the 600 mg tablets show slightly variable results for assay, but no trends are observed. No trends or changes are seen in any of the other parameters at both storage conditions. A photostability study showed that the product should be stored protected from light. The claimed shelf-life of 3 years with storage condition 'Store in the original package in order to protect from light' is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mifegyne 600 mg, tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to provide comparative dissolution profiles of two production-scale batches of Mifegyne 600 mg tablets. The two batches must be compared with the biobatch.
- The MAH committed to provide batch analysis data on a third production-scale batch.
- The MAH committed to test the third production batch of the drug product for microbial quality to fully justify non-routine testing of microbial quality.
- The MAH committed to place the first production batch post approval on stability under long-term and accelerated storage conditions.
- The MAH committed to finish the on-going stability studies. The results of the on-going stability studies at least up to the claimed shelf-life should be submitted as soon as available.
- The MAH committed to validate the manufacturing process on three production-scale batches post approval.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since the dose and indication are the same as for the already authorized 200 mg tablet, this formulation can be considered to replace the same doses for the same indication as the already registered tablet. Environmental exposure is not considered to change due to authorization of this line extension. Further environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The MAH provided an extensive overview, referring to internal reports and literature. Since the dose and indications have not been changed compared to the current 200 mg tablet, the application has not undergone additional preclinical assessment, which is acceptable for this type of application.
The non-clinical overview is considered adequate. It sufficiently discusses existing information regarding pharmacology, pharmacokinetics and toxicity of mifepristone, and the impurities in this specific product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mifepristone is a well-known active substance with established efficacy and tolerability. The active substance is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors, thus antagonising the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri.

An adequate clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. Reference to the existing Mifegyne authorisation is justified.

In support of this line extension, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Mifegyne 600 mg is compared with the pharmacokinetic profile of the reference product Mifegyne 200 mg administered as three tablets concomitantly; both are products of Exelgyn France.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design
A single-dose, randomised, two-stage, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 22-51 years. The study had a two stage design: 12 subjects were dosed in the first stage and 24 in the second stage.
Each subject received a single dose (1 x 600 mg tablet or 3 x 200 mg tablet) of one of the 2 mifepristone formulations. The dosing periods were separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0:15, 0:30, 0:45, 1, 1:15, 1:30, 1:45; 2, 2:30, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable. The volunteers were males only, to eliminate the risk of including women of childbearing potential. Mifepristone may be taken without reference to food intake. The bioequivalence study under fasting conditions is therefore appropriate. The washout period is long enough to exclude the pharmacokinetic carry-over effect, when the elimination half life of 18 hours is taken into account. The 72-sampling period is long enough to cover the absorption period appropriately.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
The interim evaluation of the results of the first 12 volunteers (1st stage) revealed that a total sample size of 36 volunteers (including the first group of 12 volunteers) was needed for reaching a power of at least 80% for proving bioequivalence of both products.

Results
All 36 subjects completed the study and were included in the pharmacokinetic and safety analyses.

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

Treatment N=36	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	71423 ± 18400	2459 ± 814	0.50-24	--
Reference	69361 ± 23276	2576 ± 929	0.50-48	--
***Ratio (90% CI)**	1.06 (0.99-1.12)	0.97 (0.91-1.03)	--	--
CV (%)	15.45	15.41	--	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life				

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study one tablet of Mifegyne 600 mg is considered bioequivalent with three tablets of Mifegyne 200 mg.

Both tablets were well tolerated. No adverse events or serious adverse events were registered in any of the 36 volunteers. The results of safety, clinical and laboratory examinations gave no indications for adverse events or adverse drug reactions.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

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 Mifegyne tablets.

It is accepted that no risk minimisation measures, except routine pharmacovigilance, are necessary for Mifegyne.

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Summary of planned minimisation activities for Mifegyne® 600 mg			
Safety concern	**Routine Risk minimisation sufficient?**	**If yes, Description of routine activity and justification**	**Additional risk minimisation measures**
Important Identified Risk			
Not applicable	Not applicable	Not applicable	Not applicable
Important Potential Risk			
Teratogenicity	YES	This event is kept under surveillance, as it has been shown to occur after failed MToP performed with mifepristone with associated PGs. Often, mifepristone and/or misoprostol use outside the labelling recommendations has occurred in these cases. Very rare cases of malformation have been reported following mifepristone administration only (without PG) and most often with confounding factors. Therefore data are too limited to determine whether mifepristone is a human teratogen. It is listed as a risk in the labelling of Mifegyne®. Action: Routine pharmacovigilance activities.	No additional risk minimisation measures are required
Important Missing Information			
Not applicable	Not applicable	Not applicable	Not applicable

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with Mifegyne 200 mg tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the registered 200 mg strength. One tablet of 600 mg can be administered instead of three Mifegyne 200 mg tablets. Risk management is adequately addressed.

V. USER CONSULTATION

Readability testing on the package leaflet (PL) has not been performed. This is considered acceptable since:

- the package leaflet of Mifegyne 600 mg had been based on the tested PL of Mifegyne 200 mg. Results of this testing have been submitted and accepted.
- no significant change to the PL of Mifegyne 600 mg in comparison with the leaflet of Mifegyne 200 mg is proposed;
- all physical characteristics of the Mifegyne 600 mg leaflet will be the same as in the current, approved leaflet of Mifegyne 200 mg.

The changes proposed in this application do not classify as significant changes, as they mainly concern correction of typos, clarification of wording, addition of adverse events that are already warned for (uterine rupture). Furthermore, there are no changes to the layout of the leaflet. The member states agree that bridging to the approved leaflet is acceptable. No separate user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mifegyne 600 mg tablets has a proven chemical-pharmaceutical quality and is a legitimate line extension to Mifegyne 200 mg tablets. Mifegyne is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence between the 600 mg tablet and 3 separate 200 mg tablets has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the Mifegyne 600 mg tablet strength is approvable as a line extension to the 200 mg, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached