CBG MEB

Public Assessment Report

Scientific discussion

Mifegyne 600 mg, tablets

(mifepristone)

NL/H/2937/001/DC

Date: 20 January 2026

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 'steps taken after finalisation' at the end of this PAR.

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 the 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

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/2937/ 002/IA/021	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority"	Yes	16-1-2014	Rejected	
NL/H/2937/ 002/IB/022	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority"	Yes	15-4-2014	Approved	
NL/H/2937/ 002/II/023	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier • Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier"	No	5-12-2014	Approved	
NL/H/2937/ 002/IA/024	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) • Change that affects the product information"	Yes	14-12-2014	Approved	
NL/H/2937/ 001/II/026	Change in the shelf-life or storage conditions of the finished product • Extension of the shelf life of the finished product Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines"	Yes	6-3-2015	Approved	
NL/H/2937/ 001/II/025	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active	No	20-3-2015	Approved	

	substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier				
NL/H/2937/ II/020/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Yes Yes	25-3-2015	Approved	
NL/H/2937/ 002/R/003	Renewal		23-3-2017	Approved	
NL/H/2937/ 001/IA/027	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan • Implementation of wording agreed by the competent authority	No	21-4-2017	Approved	
NL/H/2937/ 001/IB/028	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Introduction of an ERA	Yes	5-7-2018	Approved	
NL/H/2937/ 002/IB/029	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products Other variation	Yes	5-7-2018	Approved	
NL/H/2937/ 001-002/P/001	Update of Labelling text sections 17 and 18	Yes	3-9-2018	Approved	
NL/H/2937/ 001/E/005	Repeat Use – AT, BE, CZ, ES, IE and LU		17-11-2018	Approved	
NL/H/2937/ 002/E/004	Repeat Use – CY, HR and IE		10-12-2018	Approved	
NL/H/2937/ 001/R/004	Renewal		30-7-2019	Approved	
NL/H/2937/ 001-002/IA/031	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	Yes	1-4-2019	Approved	
NL/H/2937/ 002/IB/030	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation	Yes	18-4-2019	Approved	
NL/H/2937/	Change in manufacture of the Finished	No	18-12-	Approved	

001/IB/032	Product • Other variation		2019		
NL/H/2937/002/R/005	Renewal		17-1-2020	Approved	
NL/H/2937/001/IB/033	Change in manufacture of the Finished Product • Other variation	No	25-2-2020	Approved	
NL/H/2937/001-002/IA/034	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)	No	9-9-2020	Approved	
NL/H/2937/001-002/IA/035	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance • Up to 10-fold increase compared to the originally approved batch size	No	10-9-2020	Approved	
NL/H/2937/001-002/IB/036	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance • other variation	No	5-11-2020	Approved	
NL/H/2937/001-002/IA/039	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • The aim of this type IAin -C.I.3.a) variation is to implement the outcome of the PRAC Assessment Report on the PSUR(s) for mifepristone, following the wording proposed on the PSUSA. These information concerned the addition of a new adverse event “Acute generalised exanthematous pustulosis” in sections 4.8 on the SmPC with frequency “Unknown”, and a warning on severe cutaneous adverse reactions in section 4.4.	Yes	25-6-2021	Approved	
NL/H/2937/002/IB/040	Change in the shelf-life or storage conditions of the finished product Change in storage conditions of the finished product or the diluted/reconstituted product	No	17-7-2021	Approved	

NL/H/2937/001-002/II/038	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier • Introduction of a manufacturer of the active substance supported by an ASMF	No	12-8-2021	Approved	
NL/H/2937/001-002/II/037	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority. The aim of this variation is to submit the ERA, which is a commitment made after the assessment of variations NL/H/2937/001/IB/028 and NL/H/2937/001/IB/029	No	14-10-2021	Approved	
NL/H/2937/001/IA/041	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • Manufacturer responsible for batch release	Yes	21-12-2021	Approved	
NL/H/2937/001-002/IB/044/G	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier) Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance • Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent	No Yes No No	16-2-2022	Approved	

	used in the manufacturing process of the active substance • other variation				
NL/H/2937/001/IB/042	Change in the shelf-life or storage conditions of the finished product • Change in storage conditions of the finished product or the diluted/reconstituted product	Yes	24-2-2022	Approved	
NL/H/2937/001-002/IA/045	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance • Tightening of specification limits	No	18-7-2022	Approved	
NL/H/2937/001-002/II/043	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Yes	22-7-2022	Approved	
NL/H/2937/002/E/005	Repeat Use - IS		21-10-2022	Approved	
NL/H/2937/002/E/006	Repeat Use – LT		19-12-2022	Approved	
NL/H/2937/001-002/IA/046	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority	Yes	8-7-2024	Approved	
NL/H/2937/1-2/IA/048	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) Manufacturer responsible for batch release	Yes	21-5-2025	Approved	
NL/H/2937/001-002/II/047	Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority to fulfil a commitment taken during the RtQ to the updated ERA approved on 14/10/2021 (variation NL/H/2937/001-002/II/0037) for which a new Fish Full Life Cycle Study (FFLC) on mifepristone should be submitted following a protocol reviewed by the CBG-MEB experts.	No	28-8-2025	Approved	

Annex 1 – Submission of Updated Environmental Risk Assessment and Fish Full Life Cycle Study (NL/H/2937/001-002/II/0047)

I. RECOMMENDATION

Based on the review of the data, the RMS considers that the variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Mifegyne 200 mg and 600 mg (mifepristone), in the treatment of medical termination of developing intra-uterine pregnancy, for the following proposed changes to update the Environmental Risk Assessment (ERA).

is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The aim of this type II variation is to fulfil a commitment taken during the RtQ to the updated ERA approved on 14/10/2021 (variation NL/H/2937/001-002/II/0037) for which a new Fish Full Life Cycle Study (FFLC) on mifepristone should be submitted following a protocol reviewed by the CBG-MEB experts.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

III.2.1 Environmental risk assessment

III.2.1.1 ERA in the previous procedure - summary

In 2018, the MAH's dossier and ERA of the active ingredient mifepristone were assessed in procedure NL/H/2937/002/E/004, leading to the MAHs' commitment to perform the following studies and update the ERA accordingly:

- Partition Coefficient (1-Octanol/Water): Slow-Stirring Method (OECD 123)
- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge
- Ready biodegradability test (OECD 301)
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)
- Algal growth inhibition test (OECD 201), limit test
- Daphnia sp. reproduction test (OECD 211, version 2012)
- Activated sludge, respiration inhibition test (OECD 209, version 2010), limit test
- Fish Full Life Cycle Test. At least 5 test concentrations should be tested in order to be able to derive a valid NOEC/EC10 value for risk assessment
- Bioaccumulation in fish study (OECD 305)

In 2021, the MAH submitted in procedure NL/H/2937/001/II/037 the committed studies and provided an updated ERA based on the EMEA/CHMP/SWP/4447/00 guideline. The assessor concluded that mifepristone is considered not to be PBT, nor vPvB. It was also concluded that a risk to the STP, groundwater, sediment and terrestrial compartments is not anticipated based on the prescribed use of

mifegyne. No conclusion could be drawn for the surface water compartment as the submitted fish full life cycle (FFLC) study conducted with zebrafish (*Danio rerio*) was rejected due to the poor quality of the study itself, while also not following relevant OECD guidelines. A new fish full life cycle study was requested, to which the MAH committed.
The MAH has now submitted the committed fish full life cycle study according to the draft OECD test guideline for zebrafish (Zebrafish Extended One Generation Reproduction Test; ZEOGRT), as well as a fish, early life stage toxicity test (FELS) with zebrafish according to OECD 210. The latter study was conducted to determine the dosing of the main study. The MAH also updated the ERA based on the EMEA/CHMP/SWP/4447/00 guideline.

III.2.1.2 Result of new submitted studies
The RMS has evaluated the studies. Brief summaries are given below, extended summaries can be found at the end of this assessment (section III.2.1.5).

The fish, early life stage toxicity test with zebrafish according to OECD 210 was assessed as reliable without restrictions (Ri=1) and yielded a NOEC of 7.11 µg/L (mean measured) based on body weight.

The fish full life cycle study with zebrafish according to the draft OECD test guideline for the Zebrafish Extended One Generation Reproduction Test (ZEOGRT) yielded a NOEC of 1.03 µg/L (mean measured) based on larval mortality in the F1 (day 2 to 35). However, the assessor noted a very low egg production in the F1, i.e. 1 ± 1 and 4 ± 4 eggs/female/day in the control, respectively, solvent control, but also in the F0, i.e. 6 ± 2 and 15 ± 10 eggs/female/day in the control, respectively, solvent control. As stated in the related test guideline for the Medaka Extended One Generation Reproduction Test (OECD 240), a low number of eggs may indicate immature, malnourished or unhealthy spawning pairs, and a validity criterion of >20 eggs/female/day is maintained for studies with medaka. It is noted that ordinarily in the ZEOGRT a lower number of eggs is deemed acceptable, with the validity criterion for fecundity being set at >10 eggs/female/day. Previously, in the rejected study (Study Number 136741235) the MAH defined a test acceptance criterion for fecundity, i.e. : "*On average, at least 10 eggs per female and day should be counted in the control groups (negative and solvent control). Fertility should be at least 70 %.*". It is unclear why this validity criterion has been omitted by the MAH from the current report, as for example in section 6.4 of the ZEOGRT report it is clear that the same limit was considered, i.e.: "*When fish of sufficient test vessels had achieved a daily spawning of at least 10 eggs per female and fertilisation rates equal to or above 80 %, the exposure phase was started*". Considering the very low fecundity in the F1, but also the F0, of this study, a new study should be conducted to derive reliable and relevant endpoints. This is the 2nd fish full life cycle study submitted by the MAH, and taking animal welfare and proportionality into account, an opportunity to reflect on the serious issue identified and explain why the fecundity validity criterion was not considered, before a final conclusion is reached is granted.

III.2.1.3 Updated ERA
The MAH submitted an updated ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006). As previously the PBT assessment and the STP, groundwater, sediment and terrestrial compartments were concluded, only the surface water compartment will be presented below.

In the previous procedure, a refined $PEC_{surface\ water}$ of 0.0054 µg/L was derived. As discussed in the section above, a serious issue has been identified in the submitted fish full life cycle with fecundity not meeting the validity criterion of >10 eggs/female/day. The MAH is requested to reflect on the serious issue identified and explain why the fecundity validity criterion was not considered, before a final conclusion is reached.

III.2.1.4 Conclusion on ERA assessment

Summary of main study results for mifepristone

Substance (INN/Invented Name): mifepristone					
CAS-number (if available): 84371-65-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Log D_{ow} of 4.9 (ion corrected)			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}	4.86			
	BCF	24.8			not B
Persistence	ready biodegradability	not readily biodegradable			
	DegT50, parent	$DT_{50, system}$ = 212/282 d (p/r)			r=river; p =pond; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥746 µg/L ≥985 µg/L To be determined			conclusion: P.M.
	CMR	not investigated			potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, refined (prevalence)	0.0054	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)	potentially endocrine disrupting				focussed phase II required
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =917L/kg (loamy sand) 1542 L/kg (loam) 1838 L/kg (clay) 3391 L/kg (sludge) 2967 L/kg (sludge)			Geometric mean for soil: 1375 L/kg Geometric mean for sludge: 3063 L.kg
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ = 100 d (loam, pond) 133 d (sand, river) Sediment shifting 47.5% at day 14 (loam) 26.8% at day 14 (sand)			DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	>746	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	>985	µg/L	reproduction and mortality
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	7.11	µg/L	body weight
Zebrafish Extended One Generation Reproduction Test/*Danio rerio*	draft OECD test guideline	NOEC	to be determined	µg/L	to be determined
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥100 000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Danio rerio*	OECD 305	BCF	24.8	L/kg	lipids: 5%, growth corrected

Conclusions on studies for mifepristone:
Mifepristone is considered not to be PBT, nor vPvB.

A risk to the STP, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of Mifegyne.

The ERA cannot be finalised for the surface water compartment. The MAH is requested to reflect on the serious issue, i.e. very low fecundity in the F1 and F0, identified in the submitted fish full life cycle with zebrafish, and explain why a fecundity validity criterion was not considered, as was done in the previously conducted fish full life cycle test (Study Number 136741235). Depending on the MAHs' response a new fish full life cycle test might be required.

III.2.1.5 Extended study summaries

Chronic toxicity

Substance	Species	Method	T [°C]	pH	Hardness $CaCO_3$ [mg/L]	Duration [d]	Criterion	End-point	Value [µg/L]	Ri
mifepristone	*Danio rerio*	FT	25.5-26.2	7.0-7.9	142.4-178.0	5	NOEC	hatching	>238	1
mifepristone	*Danio rerio*	FT	25.5-26.2	7.0-7.9	142.4-178.0	34	NOEC	survival	27.5	1
mifepristone	*Danio rerio*	FT	25.5-26.2	7.0-7.9	142.4-178.0	34	NOEC	body length	>238	1
mifepristone	*Danio rerio*	FT	25.5-26.2	7.0-7.9	142.4-178.0	34	NOEC	body weight	7.11	1

FT, flow-through; -, data not provided in the study report.

Reference

Study No. 136741232 (2023)

Guideline

OECD 210 (version 2013)

Principle of method

A GLP-compliant fish early-life stage (ELS) test was performed with mifepristone (purity 100.0 %) on Zebrafish (*Danio rerio*) under continuous flow conditions. The test substance was prepared using the auxiliary solvent dimethylformamide (DMF). Nominal concentrations of 3.17, 11.1, 38.8, 136 and 475 µg/L (spacing factor 3.5) were used, each in 20 µL DMF/L. Control and solvent control (20 µL/L) groups were also included. Four replicate test vessels were prepared for the control groups and for each test substance concentration. Twenty-five fertilised eggs were added to each replicate. Light regime was 16:8 h light:dark. Brine shrimp Nauplii and flake food were fed *ad lib*. The duration of the test was 28 days post-hatch. The eggs/embryos were assessed daily for survival, and at the end of the test the lengths, and wet and dry weights of all surviving fish were assessed. The test item concentrations in the test water taken at start and after 7, 14, 21, 28 and 34 days were analysed with LC/MS.

Results

Average recoveries of 55%, 66%, 71%, 62% and 49% were determined for the nominal test concentrations of 3.17, 11.1, 38.8, 136 and 475 µg/L, respectively. These recoveries correspond to time-weighted arithmetic (TWA) mean measured concentrations of 1.64, 7.11, 27.5, 83.4 and 238 µg/L, respectively. The survival of fertilised eggs was 99.0 % in the control and 100.0 % in the solvent control. Hatching was affected at all test concentrations. The post hatch survival was 79.8 % in the control and 94.0 % in the solvent control. The number of surviving fish in the treatment groups during the 30 days post hatch exposure was not statistically significantly reduced compared to the solvent control up to and including

the measured concentration of 27.5 µg/L. At the concentrations of 83.4 and 238 µg/L, the number of surviving fish was statistically significantly reduced compared to the solvent control. The mean total length of fish (at age of 30 DPH) was 15.231 mm in the control, 14.933 mm in the solvent control and between 14.845 and 15.292 mm in the treatment groups. There was no statistically significant difference between the treatment groups and the pooled controls. The mean wet weight per fish for the control was 32.637 mg and 31.967 mg for the solvent control. The mean wet weight of larvae in the test item treatment groups ranged between 29.385 and 32.359 mg. There was a statistically significant difference between the top three treatment groups and the pooled controls. The mean dry weight per fish in the control was 7.516 mg and 7.269 mg for the solvent control. The mean dry weight of larvae in the treatment groups ranged between 6.909 and 7.456 mg. There was no statistically significant difference between the test item treated groups and the pooled control. The MAH reported for hatching success a NOEC of ≥238 µg/L, for survival a NOEC of 27.5 µg/L, for body length a NOEC of ≥238 µg/L, for body weight (based on wet weight) a NOEC of 7.11 µg/L, and for body weight (based on dry weight) a NOEC of ≥238 µg/L, respectively. The MAH noted that no reliable EC_{50} or EC_{10} values could be calculated due to the poor dose-response observed.

Remarks

Validity criteria were met. Hatching amounted to 99.0% and 100.0% in the control, respectively, solvent control (must be >70%); post hatch survival amounted to 79.8% and 94.0% in the control, respectively, solvent control (must be >75%); water temperature differed not more than ±1.5°C between the test vessels or between successive the days at any time during the test; and dissolved oxygen concentration stayed >60% of air saturation, except on day 20. It is noted that a range-finding test was not conducted and that a higher spacing factor than the recommended maximum spacing factor of 3.2 was used. This is considered acceptable, as this FELS test was used as a pre-test for a fish full life cycle study. It is noted that the poor-dose response allowed only to derive NOEC values and not EC_x values. According to OECD TG 210, wet weight is preferred for body weight. Therefore, the lowest NOEC of 7.11 µg/L is used for conclusions. The results of this study are considered reliable (Ri=1).

Chronic toxicity

Substance	Species	Method	T [°C]	pH	Hardness $CaCO_3$ [mg/L]	Duration [days or dpf]	Criterion	Endpoint	Value [µg/L]	Ri
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 21	NOEC	fecundity	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 21	NOEC	fertility rate	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	VTG, m	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	VTG, f	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body weight, m	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body length, m	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body weight, f	4.18	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body length, f	13.1	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Ghistology	>45.6	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 5	NOEC	hatching	>38.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 35	NOEC	survival	1.03	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 35	NOEC	Body length	>38.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 63	NOEC	Body length	10.9	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 63	NOEC	survival	>38.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	survival	>36.5	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	fecundity	11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	fertility rate	11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	VTG, m	>36.5	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	VTG, f	>11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	Body weight, m	11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	Body weight, f	>11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Body length, m	11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Body length, f	>11.2	tbd
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Sex ratio	11.2	tbd

Substance	Species	Met T hod [°C]		pH	Hardness $CaCO_3$ [mg/L]	Duration [days or dpf]	Criterion	Endpoint	Value [µg/L]	Ri
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F2	NOEC	hatching	3.4	tbd

dpf, days post fertilisation; FT=flow-through; VTG, vitellogenin, f-female, m-male, Ghistology, Gonad histology; tbd = to be determined

Reference

Study No. 136741235 (2024)

Guideline

draft OECD test guideline for a Zebrafish Extended One Generation Reproduction Test (ZEOGRT), which is currently under OECD Phase II validation.

Description

A GLP-compliant fish full life cycle study was performed with mifepristone (purity 100.0 %) on zebrafish (*Danio rerio*) under the flow-through condition. The nominal concentration range used for the definitive test was 0.38, 1.22, 3.91, 12.5 and 40 µg/L, which was based on the above assessed FELS test (Study No. 136741232, 2023), with the measured LOEC value of 27.5 µg/L based on body weight (wet weight). The test substance was prepared using the auxiliary solvent dimethylformamide (DMF). Control and solvent control (20 µL/L) groups were also included. Prior to test start, the fish groups were held under test conditions to record spawning success during the pre-exposure phase. Following the pre-exposure period of 26 days, actively spawning adults (F0 generation) were introduced into the test system. Five males and five females were added to each test vessel. Four replicates were established for each test concentration along with water and solvent control groups. The duration of the F0 generation exposure phase was 21 days. The fish were observed daily throughout the exposure period for survival and general behaviour. After the 21-day reproduction phase, and once the F1 generation had been established, all the fish were euthanised at 57-58 days for F0. Mortality, behaviour, fecundity, fertility, wet weight, standard length, vitellogenin concentration (blood samples), were determined for F0. The zebrafish in the controls and the treatment groups did not spawn sufficiently on two consecutive days after the 21 days of exposure. Fertilised eggs from the respective replicates were used wherever possible (20 out of 28 replicates). In case that fish have not spawned in a replicate over two consecutive days, the eggs from the remaining replicates of the same treatment were mixed and 36 fertilised eggs were chosen at random to avoid bias (8 out of 28 replicates). Fertilised eggs were randomly distributed into each replicate of the control and each test concentration to give a 36 eggs per replicate and 144 eggs per test concentration. The post-hatch phase started once all of the viable eggs were considered to have hatched. At the start of the post-hatch phase an initial estimate of hatching success was made. On day 21, 28, 35 and 63 post fertilisation, survival was determined by photographic counting. At the end of the early life stage phase (day 35 post fertilisation of the F1 generation), the individual length of all surviving fish was determined via photographic measurements. On day 35 post fertilisation, fish were randomly reduced to 20 individuals to create identical conditions for reproduction in each test vessel. On day 63 post fertilisation, the individual length of juvenile fish was determined via photographic measurements. Parental fish of the F0 and F1generation were measured and weighted after the termination of the respective reproduction phases. Fish blood was sampled for vitellogenin via cardiac puncture. The measurement of VTG was conducted with a validated ELISA method and commercially available zebrafish-specific ELISA vitellogenin test kits. Wet weight and standard length measurements were performed for each individual fish. Whole fish were placed in Davidson's fixative. The histopathological investigations with fixed tissue excluding the head were performed to determine the sex ratio in the controls and treatment groups and to assess the reproductive fitness and the gonadal stage of the exposed animal. In the F1 generation reproductive exposure phase, the F2 generation was initiated. The eggs were randomly distributed to give a maximum

of 20 eggs per replicate. Once hatching was complete in all vessels, the test was terminated. The test was conducted in a light-controlled facility, with a 16-hour light:8-hour dark period with an approximate 30-minute dawn:dusk transition period. The temperature, pH and concentration of dissolved oxygen of each test vessel were determined at the start and end of the test and then weekly throughout the duration of the test in a single replicate per concentration. Temperature was also monitored continuously in one of the control vessels. Fish were fed ad libitum with commercially available flake food (TetraMin) in the morning, brine shrimp (artemia nauplii) at midday, and in the afternoon. Thus, feeding was conducted three times daily during pre-exposure phase and exposure phase. In this study, Phase I included a pretreatment period of 26 days and a treatment period of 58 days in F0; phase II covered the embryonic development through the juvenile phase of the F1 generation, up to 63 days post-fertilisation (dpf). Phase III spanned from 63 dpf until the termination of F1 at 171 dpf, including additional F2 exposure. Analytical verification of the test item concentrations was performed for samples taken during Phase I at day 0 (test start), 7, 14, 21, 27, 35, 42, 49 and 56 (end of Phase I = termination of F0 generation), during Phase II at day 1 (introduction of eggs of F1-Generation), 7, 14, 21, 28, 35, 42, 49, 56, 63 and during Phase III at day 65 (introduction of juvenile fish of F1 generation), 71, 77, 85, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 167, 168, 170, 171 of the F1 generation. The quantification of mifepristone was performed using liquid chromatography with MS/MS detection.

Results

Concentrations in the test solutions were not maintained within ± 20% of the mean measured values. The time-weighted arithmetic (TWA) mean measured concentrations for the nominal test concentrations of 0.38, 1.22, 3.91, 12.5 and 40.0 µg/L were 0.415, 1.37, 4.18, 13.1 and 45.6 µg/L in phase I; 0.319, 1.03, 3.23, 10.9 and 38.2 µg/L in phase II, and 0.296, 1.01, 3.40, 11.2 and 36.5 µg/L in phase III, respectively. The results of this study for each phase are based on their respective time-weighted mean measured concentrations.

F0--results

For the first 21 days of exposure, no mortality was observed in the fish of the control, the solvent control, and in the test concentrations of 0.415 and 13.1 µg/L. One fish died in each treatment group of 1.37, 4.18, and 45.6 µg/L, resulting in a treatment mortality of 2.5 % after 21 days of exposure. From day 22 of exposure until the termination of the F0-Geneneration (day 57-58), no mortality was observed in the fish of the control, the solvent control. No significant difference was found for mortality in the test item concentrations and the solvent control. No significant difference was found in fecundity, fertility rate, male and female VTG, male wet weight, and male body length. A significant decrease in female body weight was found in the 13.1 and 45.6 µg/L groups. A significant difference was found in female body length in the 45.6 µg/L group. There were no differences in ovarian and testicular stages and histopathological changes.

F1--results

No difference was reported for hatching success. A significant decrease in survival was found for larvae at dpf 35 for the 3.23, 10.9 and 38.2 µg/L groups. No significant difference was found for survival (dpf 36 – 63; and 64-termination) between the test concentrations and the solvent control. No significant difference was found for body length at day 35 between the test item concentrations and the solvent control. A significant decrease in body length was found for the top concentration group at day 63 and at the termination of F1. A significant difference in male wet weight was found for the highest treatment group of 36.5 µg/L at the termination of F1. A significant decrease in fecundity was found for the 36.5 µg/L group.

No significant difference was found for fertility up to 11.2 µg/L. Fertility in the highest treatment group of 36.5 µg/L could not be determined due to no eggs. No significant difference was found for male and

female VTG between the solvent control and treatment groups in F1. Since only one female was found in the highest treatment group of 36.5 µg/L, it was not considered reliable for the statistical analysis of female VTG and body weight and length. The sex ratio between male and female fish showed a statistically significant increase in male fish for the highest test item concentration of 36.5 µg/L.

F2--results

The number of coagulated eggs observed in the control and the solvent control were 3 and 6, respectively. The number of coagulated eggs in the test concentrations of 0.296, 1.01, 3.40, and 11.2 µg/L was 4, 7, 0 and 38, respectively. The high number of coagulated eggs in the test concentration of 11.2 µg/L was due to microbial growth and not due to the test substance exposure. The hatching success was 95.0, 88.8, 100.0 and 52.5 % for the test concentrations of 0.296, 1.01, 3.40, and 11.2 µg/L, respectively. The low percentage of hatching success in the test concentration of 11.2 µg/L was due to microbial growth and not due to the test substance exposure. No eggs were observed in the test concentration of 36.5 µg/L.

MAH conclusions

The MAH concluded that the most sensitive endpoint regarding endocrine disruption is the change in sex ration towards males in the F1 generation with a NOEC of 11.2 µg /L (mean measured; nominal 12.5 µg /L). The MAH also noted that a decrease in fecundity in the F1 generation yielding a NOEC of 11.2 µg /L (mean measured), is considered supporting.

The MAH further discarded several lower NOECs as being not biologically relevant and within range of biological variability, including the most sensitive biological endpoint of larval mortality (day 2 to 35) that yielded a NOEC of 1.03 µg/L (mean measured; nominal 1.22 µg/L) and the reduced female wet weight in the F0 generation yielding a NOEC of 4.18 µg/L (mean measured; nominal 3.91 µg /L).

There is no OECD test guideline for the Zebrafish Extended One Generation Reproduction Test (ZEOGRT). The MAH described in section 6.10 of the study report the following test acceptance criteria:

(i) Fertility: The fertility of eggs from control fish should be greater than 80 %.

(ii) Hatchability: The hatchability of embryos from control fish should be greater than 80 %.

(iii) Post-Hatch Survival (Early Life Stage Phase of F1-Generation): Post-hatch survival of fish larvae, fry and juveniles should be greater than or equal to 75 % during the early in the controls. Overall survival of fish larvae, fry and juveniles must be at least 75 % in the controls.

(iv) Spawning Condition: Fish should be actively spawning in all replicates of the controls prior to initiating the reproduction phase.

(v) Sex Ratio: The sex ratio in the controls should preferably be between 30 and 70 %.

(vi) Overall Survival: There should be more than 90% survival of juvenile and adult control fish in all test phases over the duration of the chemical exposure.

(vii) Water Temperature: During exposure period the water temperature should not differ by more than 26 ± 1.5 °C between the test vessels at any time and should be maintained within a range of 1.5 °C.

(viii) Dissolved Oxygen Concentration: The dissolved oxygen concentration in the test media should be at least 60 % of air saturation value during the test;

(ix) Analytical Measurement: The analytical measurement of the test concentrations is compulsory. Evidence should be available to demonstrate that the concentrations of the test item in solution have been satisfactorily maintained within ±20% of the mean measured values. In case the

measured concentrations do not remain within 80-120% of the nominal concentration, the effect concentrations should be determined and expressed relative to the arithmetic mean concentration for flow-through tests.

In absence of a definitive protocol for the ZEOGRT, comparison can only be made to the validity criteria specified in the Medaka Extended One Generation Reproduction Test (MEOGRT; OECD 240), thereby taking into account the species differences as specified in Annex 2 to FELS (OECD 210), i.e. a minimum hatching success of 80% in medaka and 70% in zebrafish, and a minimum post-hatch success of 80% in medaka and 75% in zebrafish, respectively. While in the MEOGRT it is stated that >65% of the breeding pairs should produce >20 eggs per pair per day, the MAH did not define an acceptance criterion for fecundity in this test. Previously, in the rejected study (Study Number 136741235) the MAH did define a test acceptance criterion for fecundity: "*On average, at least 10 eggs per female and day should be counted in the control groups (negative and solvent control). Fertility should be at least 70 %*.". The assessor notes that for ZEOGRT ordinarily the validity criterion is set at >10 eggs per female per day in the control group, as was done previously. It is unclear why this validity criterion has been omitted from the current report, as for example in section 6.4 of the current report it is clear that the same limit was considered, i.e.: "*When fish of sufficient test vessels had achieved a daily spawning of at least 10 eggs per female and fertilisation rates equal to or above 80 %, the exposure phase was started*". With regard to the other proposed test acceptance criteria, these can be accepted as validity criteria.

Most of the above noted acceptance criteria were met, or in cases they were not met this was not considered an issue, except for the fecundity criterion.

The mean fecundity for control and solvent control was 6 ± 2 and 15 ± 10 eggs/female/day, respectively, during the first 21 days of exposure in F0. The mean fertility rate for control and solvent control was 77.0 ± 13.5 % and 89.6 ± 4.6 %, respectively, during the first 21 days of exposure in F0. The mean fecundity for control and solvent control was only 1 ± 1 and 4 ± 4 eggs/female/day, respectively, during reproduction phase (day 147 – 167) of the F1 generation. The mean fertility rate for control and solvent control was 68.0 ± 23.3 % and 65.8 ± 12.8 %, respectively, during reproduction phase (day 147 – 167) of the F1 generation. Thus the validity criterion of >10 eggs per female per day in the control group was not met for the control in the F0 and for the control and solvent control in the F1. As detailed in OECD 240, the low egg production may indicate immature, malnourished or unhealthy spawning pairs, and failure of this validity criterion is considered a critical issue. Consequently, a new study is needed to derive reliable and relevant endpoints.

The significant changes in sex ratio indicate that this substance is an endocrine disruptor. Despite the respective endpoints being significantly affected, it is not possible to discard more sensitive endpoints as not being biologically relevant,. Particularly, the lowest NOEC of 1.03 µg/L (mean measured; nominal 1.22 µg/L) based on larval mortality (day 2 to 35) in the F1.

Only four treatment groups are available for F2 testing because no eggs were available at the highest test concentration. The MAH stated that the low hatching success and the high number of coagulated eggs at 11.2 µg/L group were due to microbial growth and not due to the test substance exposure. However, the MAH did not provide strong evidence to exclude substance effects in this group. Therefore, the effects at this concentration are considered substance related and a NOEC of 3.4 µg/L (mean measured; nominal 3.91 µg/L) is derived.

Considering all above, taking animal welfare and proportionality into account, and considering this is the 2nd study submitted by the MAH, the assessor is willing to provide the MAH an opportunity to reflect on the serious issue, i.e. very low fecundity in the F1 and F0, identified in the submitted fish full life cycle with zebrafish, and to explain why a fecundity validity criterion was not considered, as was done in the previously conducted fish full life cycle test (Study Number 136741235), before a final conclusion is taken.

III.2.1.6 References

EMEA. 2006. Guideline on the environmental risk assessment of medicinal products for human use. London, United Kingdom: European Medicines Agency. Report nr. EMEA/CHMP/SWP/4447/00. 12 p.

2023. Mifepristone: Toxicity to Zebrafish (*Danio rerio*) in an Early-Life Stage Test, Study No. 136741232. 100 p.

2024. Mifepristone: Zebrafish (Danio rerio) in a Fish Full Life Cycle Study, Study No. 136742235. 665 p.

III.3 Clinical aspects

N/A

III.4 Product information

N/A

IV. OVERALL CONCLUSION

The efforts made by the MAH to reflect on the very low fecundity observed in the ZEOGRT. The MAH demonstrated that fish were adequately selected in the pre-exposure phase. The fecundity and fertility observed in the control groups of the F0-generation met the validity criterion for successful reproduction, being a fecundity of >10 eggs/female/day, and a fertility of 80%. The fecundity threshold of >10 eggs/female/day is an important indicator of whether fish in controls are actively spawning, not only for the F0-generation, but also for the F1-generation. A fecundity of >10 eggs/female/day was not met in the F1-generation. The draft ZEOGRT guideline, which is still in the validation phase and may be subjected to modifications till completion, does not specify the F1 fecundity as a validity criterion. Still the low fecundity in the controls might indicate that the F1 spawning pairs were unhealthy and less productive, and consequently not suitable for use in the reproductive study. While the factors identified by the MAH, such as feeding, genetic background, sex ratio, biofilm, and spawning trays, could also have impacted F1 reproduction, it cannot be excluded that the fish were unhealthy and less productive. Therefore, no conclusions can be drawn regarding F1 reproduction. Regarding F2, despite the measures taken by the MAH to reduce microbial growth, a biofilm was formed leading to low hatching success of the F2 fish. Consequently, the F2 results cannot be used for conclusions.
The issues described above should be considered as serious. However, there is sufficient information available from the study to be able to do a risk assessment based on worst case data from F1 survival. Therefore, the reliability of the study is rated as Ri=2, while the affected F1 reproduction and F2 endpoints are considered unreliable (Ri=3). Further, considering this is the second study submitted by the MAH, it is unlikely that in a further study the issues will be resolved to provide new useful information that will influence the conclusion, as F1 larval survival is likely not affected by the serious issues identified that primarily occurred during the later life stages of the F1 fish and the F2 fish. A further repeat of the study is also not in line with 3R principles. A NOEC of 1.03 µg/L, based on survival in the F1 generation is accepted, which will be used further in risk assessment. The updated study summary table is included below.

In the previous procedure, a refined PECsurface water of 0.0054 µg/L was derived. Using the lowest NOEC of 1.03 µg/L for zebra fish, a PNECsurface water of 0.103 µg/L is obtained. The RQsurface water is 0.052,

which is <1. A risk to the surface water compartment is not anticipated based on the prescribed use of Mifegyne. The ERA can be concluded. ***Issue solved***

Updated summary table of the study with mifepristone (Study No. 136741235, 2024)

Substance	Species	Met T hod [°C]		pH	Hardness $CaCO_3$ [mg/L]	Duration [days or dpf]	Criterion	Endpoint	Value [µg/L]	Ri
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 21	NOEC	fecundity	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 21	NOEC	fertility rate	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	VTG, m	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	VTG, f	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body weight, m	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body length, m	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body weight, f	4.18	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Body length, f	13.1	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F0, 58	NOEC	Gonad histology	>45.6	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 5	NOEC	hatching	>38.2	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 35	NOEC	survival	1.03	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 35	NOEC	Body length	>38.2	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 63	NOEC	Body length	10.9	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 63	NOEC	survival	>38.2	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	survival	>36.5	2
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	fecundity	11.2	3
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	fertility rate	11.2	3
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	VTG, m	>36.5	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	VTG, f	>11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	Body weight, m	11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1	NOEC	Body weight, f	>11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Body length, m	11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Body length, f	>11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F1, 171	NOEC	Sex ratio	11.2	2*
mifepristone	*Danio rerio*	FT	24.7-26.6	7.1-7.9	106.8-213.6	F2	NOEC	hatching	3.4	3

Dpf: days post fertilisation; FT: flow-through; VTG: vitellogenin, f: female, m: male; * endpoints are borderline Ri=2 due to associated uncertainties

Conclusion on ERA assessment

Summary of main study results for mifepristone

Substance (INN/Invented Name): mifepristone			
CAS-number (if available): 84371-65-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	Log D_{ow} of 4.9 (ion corrected)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	4.86	
	BCF	24.8	not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50, parent	$DT_{50,\ system}$ = 212/282 d (p/r)	r=river; p =pond; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥746 µg/L ≥985 µg/L To be determined	conclusion: P.M.
	CMR	not investigated	potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surface\ water}$, refined (prevalence)	0.0054	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)	potentially endocrine disrupting				focussed phase II required
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =917L/kg (loamy sand) 1542 L/kg (loam) 1838 L/kg (clay) 3391 L/kg (sludge) 2967 L/kg (sludge)			Geometric mean for soil: 1375 L/kg Geometric mean for sludge: 3063 L.kg
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ = 100 d (loam, pond) 133 d (sand, river) Sediment shifting 47.5% at day 14 (loam) 26.8% at day 14 (sand) $\%CO_2$ = 2.8 (loam) / 3.7 (sand) %NER = 36.8 (loam) / 60.8 (sand) Transformation products ≥ 10 %: TP Unknown 2 (DT50 not available) TP Unknown 5 ($DT50_{12°C}$ = 245.4 d) TP Unknown 6 (DT50 not available)			DT_{50} values at 20°C; Significant shifting to sediment observed. at test end at test end identities:TP2 - Metapristone, TP5 - Metapristone derivative (N-methyl nitrous amide) seems to be vP, TP6 - Metapristone derivative (Dimethylnitramine)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	>746	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	>985	µg/L	reproduction and mortality
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	7.11	µg/L	body weight
Zebrafish Extended One Generation Reproduction Test/*Danio rerio*	draft OECD test guideline	NOEC	1.03	µg/L	larval survival F1
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥100 000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Danio rerio*	OECD 305	BCF	24.8	L/kg	lipids: 5%, growth corrected

Conclusions on studies for mifepristone:

Mifepristone is considered not to be PBT, nor vPvB.

A risk to the surface water, STP, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of Mifegyne.