

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Misoprostol Exelgyn 200 micrograms, tablets
Exelgyn, France**

misoprostol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 113032

25 March 2014

Pharmacotherapeutic group:	other gynaecological drugs, oxytocics - prostaglandins
ATC code:	G02AD06
Route of administration:	oral
Therapeutic indication:	medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea
Prescription status:	prescription only
Date of authorisation in NL:	2 July 2013
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Misoprostol Exelgyn 200 micrograms, tablets from Exelgyn. The date of authorisation was on 2 July 2013 in the Netherlands.

The product is indicated for medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea. Misoprostol is indicated in adults and limited data is available on its use in adolescents.

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

Misoprostol (a synthetic analogue of prostaglandin E1) is used in combination with mifepristone for the termination of pregnancies of ≤ 49 days of amenorrhea.

In the event of an early termination of pregnancy, the combination of mifepristone-misoprostol leads to an increase in the success rate to about 95% of the cases and accelerates the expulsion of the conceptus. The success rate is around 95% when 600 mg mifepristone is combined with misoprostol 400 micrograms orally up to 49 days of amenorrhea.

This application was submitted as a line extension to the medicinal product MisoOne 400 micrograms, tablets (NL License RVG 110664), which was registered in the Netherlands on 4 December 2012 by decentralised procedure NL/H/2355/001.

This national procedure concerns a hybrid application with reference to the innovator product Cytotec 200 mcg misoprostol tablets (NL License RVG 13724), which has been registered in the Netherlands since 26 March 1990. The MAH of this product, Pfizer B.V., has never applied for the indication 'medical termination of pregnancy (ToP) in women with ≤ 49 days of amenorrhea'. Nevertheless, Cytotec is widely used off-label in this indication. In France HRA Pharma has registered 200 mcg misoprostol tablets for this indication. A formal reference to this dossier cannot be made, as it was not registered based on a full dossier application.

Cytotec is available in tablets of 100 mcg and 200 mcg. The recommended adult oral dose for reducing the risk of NSAID-induced gastric ulcers is 200 mcg 4 times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. Generics are also available.

The dosing regimen that is approved for medical ToP in the Netherlands, other European countries, and the U.S. involves 600 mg mifepristone taken orally followed 36-48 hours later by 400 mcg oral misoprostol.

As in this application the therapeutic indication differs from the innovator's, the marketing authorisation is based on a hybrid application with Cytotec as the reference product. The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application. Reference is made to the data submitted in support of the MisoOne 400 micrograms application (DCP NL/H/2355/001). The indication was supported with relevant literature data.

Furthermore, the MAH refers to a comparative bioavailability (BA) study which compared misoprostol 400 micrograms tablets by Exelgyn to Cytotec. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. A biowaiver for the 200 microgram product is acceptable. See also section II.3 'Clinical aspects'.

No scientific advice was given with regard to this application and no paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is misoprostol, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Misoprostol is a clear, colourless or yellowish, oily liquid. It is hygroscopic. Misoprostol is insoluble in water, soluble in ethanol (96%), and sparingly soluble in acetone.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH has adopted the specification for the drug substance and the corresponding analytical methods from the CEP holder. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

Stability data on the active substance has been provided for one batches stored at 2-8°C for 8 weeks. This is not sufficient and additional stability data for at least two production- or three pilot-scale batches, stored under both long term and accelerated conditions, is required. Since additional stability data is not available yet, the drug substance will be tested immediately prior to use.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Intermediate product

Instead of using the drug substance itself, an intermediate product - misoprostol dispersion (a mixture of misoprostol with hypromellose) - is manufactured first by the CEP-holder. This mixture is made in order to improve the stability of the drug substance.

The misoprostol dispersion is a mixture of misoprostol with hypromellose. The only other excipient used during the manufacturing process is ethanol (denaturated). Since the drug substance itself is not altered during this process the same impurities might be present as described for the drug substance. However in the specification for the dispersion wider limits for the impurities are applied since it is no longer a drug substance. The stability of the misoprostol dispersion has been adequately shown for up to 60 months when stored at 2 – 8°C.

Medicinal Product

Composition

Misoprostol Exelgyn contains 200 mcg of misoprostol as the active substance. It is a white, round, flat tablet, with a diameter of 8.5 mm and thickness of 3.6 mm, engraved with "M" and "200" on either side of the score line, and plain on the other side. The tablet can be divided into equal halves.

The tablets are packed in PVC/PCTFE-Alu blister or a Alu-Alu blister packs.

The excipients are: microcrystalline cellulose, hypromellose, sodium starch glycolate (type A), hydrogenated castor oil.

Pharmaceutical development

The objective was to develop an immediate-release tablet containing the same drug substance as the reference product Cytotec® 200 mcg and exhibiting the same bioavailability.

The development of the product has been described, the choice of the excipients justified and their functions explained. Manufacturing process development has been adequately described. Comparative dissolution data support that the test product is essentially similar to the reference product. Rapid dissolution was demonstrated for both the test and reference product. Similar dissolution between the 400 mcg product used in the bioequivalence study and the 200 mcg strength has also been demonstrated.

Manufacturing process

The manufacturing process consists of three blending steps, followed by compression and packaging of the tablets. The process is seen as a standard process and has been satisfactorily described.

The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

With the exception of denaturated ethanol the excipients comply with the Ph.Eur. For denaturated ethanol an in-house specification is included. The proposed specifications for the excipients are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, uniformity of dosage units, dissolution, water content, assay, related substances and microbiological quality. The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods.

Batch analysis data have been provided on two batches. Compliance with the proposed release requirements is demonstrated.

Stability of drug product

Stability data have been provided for two batches packed in PVC/PCTFE-Alu blisters and in bulk. For the proposed Alu-Alu blister only stability data up to 6 months is available.

In the PVC/PCTFE-Alu blisters the drug product has been stored at long-term conditions (25°C/60%RH; 18 months), intermediate conditions (30°C/65%RH; 12 months) and at accelerated conditions (40°C/75%RH; 6 months). The drug product is not stable at accelerated and intermediate conditions. Also under long term conditions trends are observed. Photostability was demonstrated for misoprostol 200 mcg tablets.

Based on the stability data provided, a shelf-life of 18 months when stored below 25°C when packed in the PVC/PCTFE-Alu blister, and 12 months when stored below 25°C in the Alu-Alu-blisters can be granted.

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.2 Non-clinical aspects

No new non-clinical studies were performed for the current application. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The MAH submitted an ERA. In phase I the PEC surface water was calculated as 0.002 mcg/L, and hence does not exceed the action limit for a phase II assessment. The risk to the environment can be considered negligible.

II.3 Clinical aspects

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

A clinical overview has been provided, which is based on scientific literature. The indication ToP is sufficiently discussed. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

Bioequivalence study

For this hybrid application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product MisoOne 400 mcg (Exelgyn, France) is compared with the pharmacokinetic profile of the reference product Cytotec 200 mcg (two tablets, by Pfizer B.V., NL).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products.

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

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 55 healthy female subjects, aged 20 – 45 years. Each subject received a single dose (either 400 mcg test or 2 x 200 mcg reference) of one of the 2 misoprostol formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0:04, 0:08, 0:12, 0:16, 0:20, 0:25, 0:30, 0:40, 0:50, 1:00, 1:15, 1:30, 2:00, 3:00, and 5:00 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

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.

Results

In total 51 subjects completed both periods of the study. Two subjects dropped out due to vomiting 2 hours after drug administration and two subjects were withdrawn to the adverse reactions (uterine hemorrhage).

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

Treatment N=51	AUC _{0-t} pg.h/ml	AUC _{0-∞} pg.h/ml	C _{max} pg/ml	t _{max} h	t _{1/2} h
Test	644.69 ± 298.41	660.63 ± 302.14	1011.06 ± 604.74	0.33 (0.13-3.0)	0.60

Reference	637.87 ± 288.08	657.06 ± 288.89	1057.63 ± 677.55	0.27 (0.13-0.67)	0.62
*Ratio (90% CI)	1.01 (0.96-1.06)	--	0.96 (0.85-1.07)	--	--
CV (%)	15.3	--	35.2	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of misoprostol under fasted conditions, it can be concluded that MisoOne 400 mcg and two tablets of Cytotec 200 mcg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Misoprostol may be taken without reference to food intake. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

Biowaiver

A biowaiver has been granted for the 200 mcg strength, as the following conditions are met:

- Both Misoprostol Exelgyn 200 mcg and 400 mcg tablets are manufactured by the same manufacturer and manufacturing process.
- misoprostol acid exposure in terms of C_{max} and AUC increases linear with dose in a dose range between 200 and 400 mcg.
- The qualitative composition of the different strengths is the same and quantitatively proportional as both drug products are manufactured from the same blend.
- Comparative dissolution tests of the 200 and 400 mcg tablets were conducted. In water and dissolution media with pH interval pH 4.5 and 6.8 dissolution was fast. The dissolution profiles of the different strengths are similar.

Clinical efficacy/safety

Based on the provided data, a favourable benefit/risk balance is concluded for Misoprostol Exelgyn 200 mcg. Reference is made to the registration of MisoOne 400 mcg tablets, for which a Public Assessment report is available (http://mri.medagencies.org/download/NL_H_2355_001_PAR.pdf). The literature data in support of the indication are discussed in this report.

Pharmacovigilance system

The Board considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The EU Risk Management Plan (RMP) for misoprostol is summarised in the table below:

Safety concern	Proposed Pharmacovigilance	Proposed risk minimisation
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	activities (Routine or additional)	activities (Routine or additional)
Important Identified Risk		
Misuse	Routine Pharmacovigilance Signal detection of events of interest Observational Study AMAYA Evaluation of understanding of labelling recommendations using prescription surveys (France and all other countries)	SmPC PIL Packaging Educational Material kit
Teratogenicity	Routine Pharmacovigilance Signal detection of events of interest Observational Study AMAYA Evaluation of understanding of labelling recommendations using prescription surveys (France and all other countries)	SmPC PIL Packaging Educational Material kit
Toxic & Septic shock	Routine Pharmacovigilance Signal detection of events of interest Observational Study AMAYA Evaluation of understanding of labelling recommendations using prescription surveys (France and all other countries)	SmPC PIL Packaging Educational Material kit
Uterine haemorrhage	Routine Pharmacovigilance Signal detection of events of interest Observational Study AMAYA Evaluation of understanding of labelling recommendations using prescription surveys (France and all other countries)	SmPC PIL Packaging Educational Material kit
Abdomino-pelvic pain	Routine Pharmacovigilance Signal detection of events of interest Observational Study AMAYA Evaluation of understanding of labelling recommendations using prescription surveys (France and all other countries)	SmPC PIL Packaging Educational Material kit
Uterine rupture	Routine Pharmacovigilance Signal detection of events of interest	SmPC PIL Packaging
Cardiovascular ischemic disorders	Routine Pharmacovigilance Event of interest for signal detection	SmPC PIL Educational Material kit

AMAYA is a non interventional post-approval safety study designed to collect data mainly on medical practice. The study will allow collecting data on all the safety concerns:

As written in the protocol, any SAE or AE should be reported by the investigator. Additionally, in the self questionnaire filled-in by the patient, expected AE are recorded.

In AMAYA study, the following situations are considered:

- any serious adverse events
- medication failure requiring a new abortion procedure
- lost of follow-up with unknown outcome
- on-going pregnancies (follow-up planned up to delivery)

Results obtained in the AMAYA study are an extrapolation (and not the actual data) for Misoprostol Exegyn, because Cytotec is the product that was investigated. Based on demonstrated bioequivalence of Misoprostol Exegyn with Cytotec, the safety and the efficacy profile collected for Cytotec in this study can be extrapolated. The educational materials are acceptable.

Product information

SmPC

The content of the SmPC approved during the decentralised procedure is acceptable and in accordance with the SmPC of MisoOne 400 mcg (NL/H/2355/001).

Readability test

The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PL for MisoOne 400 microgram tablets. The results can be extrapolated to Misoprostol Exelgyn 200 micrograms, since the package leaflet for Misoprostol Exelgyn 200 microgram is based on the package leaflet of the 400 microgram product. Therefore all the questions asked in the readability test for MisoOne 400 microgram apply to the 200 microgram product as well. The results of the user test were satisfactory, i.e. at least 90% of the participants were able to find the information and at least 90% were able to express the information in their own words. Separate user testing for the 200 microgram product is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Misoprostol Exelgyn 200 micrograms, tablets has a proven chemical-pharmaceutical quality and is an approvable line extension to MisoOne 400 micrograms. The product is a hybrid form of Cytotec 200 mcg misoprostol tablets. Cytotec is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents, based on extrapolation of the results obtained with MisoOne.

The therapeutic indication of Misoprostol Exelgyn differs from the innovator. Nevertheless, Cytotec is widely used off-label in the indication *medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea*. As for MisoOne, the indication is approvable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of MisoOne. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, has granted a marketing authorisation. Misoprostol Exelgyn 200 micrograms, tablets was authorised in the Netherlands on 2 July 2013.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to perform long term and accelerated testing on 3 batches of active substance. These on-going stability studies will be finished.
- The MAH committed to place at least one batch of stabilised active substance (misoprostol dispersion) on stability testing annually under the same ICH refrigerated conditions of 5 ± 3 °C.

Quality - medicinal product

- The MAH committed to re-evaluate the proposed limits when more stability data becomes available.
- The MAH committed to initiate a stability study for a batch of finished product manufactured with 6 months old misoprostol dispersion.
- The MAH committed to finish the on-going stability studies. Post-approval one additional production batch will be placed on stability conform current EC/ICH stability guidelines.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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