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M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

MisoOne 400 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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2355/001/DC
Registration number in the Netherlands: RVG 110664

29 April 2013
Updated November 2019

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:	4 December 2012
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EE, ES, FI, FR, IT, LU, LV, NO, PT, RO, SE, SI, SK, UK Through repeat use procedures the product is also registered in EL, HR, CY, IE
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.

INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for MisoOne 400 micrograms, tablets from Exelgyn. The date of authorisation was on 4 December 2012 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 µg orally up to 49 days of amenorrhea.

This decentralised procedure concerns a hybrid application with reference to the innovator product Cytotec 200 µg 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 µg 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 µg and 200 µg. Generics are also available. The recommended adult oral dose for reducing the risk of NSAID-induced gastric ulcers is 200 µg 4 times daily with food. If this dose cannot be tolerated, a dose of 100 µg can be used.

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

As in this application the therapeutic indication had changed compared to the innovator, as well as the dose, 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.

The MAH submitted literature data to support the indication as well as a comparative bioavailability (BA) study to confirm that the misoprostol tablets applied for and Cytotec have comparable bioavailability. The reference product used in the study was obtained from the Netherlands. 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.
No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

National Scientific Advice was given in the Netherlands in 2009 and 2010. The MAH followed these advices.

No paediatric development programme has been submitted, as this is not required for a hybrid application.

SCIENTIFIC OVERVIEW AND DISCUSSION

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
MisoOne contains 400 µg of misoprostol as the active substance. It is a white, round, flat tablet, with a diameter of 11 mm and thickness of 4.4 mm, with "M400" engraved on one side.

The tablets are packed in perforated unit-dose PVC-PCTFE/Alu or OPA-Alu-PVC/Alu blisters.

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

Pharmaceutical development
The objective of the applicant was to develop an immediate-release tablet containing the same drug substance as the reference product Cytotec 200 µg and exhibiting the same bioavailability. However, compared to the reference product a dose of 400 µg is proposed for the drug product, due to a different indication.
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. In all 4 media both the test batches and the reference batch dissolved rapidly (> 85% in 10 minutes).

Manufacturing process
The manufacturing process consist 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 moths is available.
In the PVC/PCTFE-Al 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 400 µg tablets.
Based on the stability data provided, a shelf-life of 12 months when stored below 25°C when packed in the PVC/PCTFE-Alu blister, and 6 months when stored below 25°C in the Alu-Alu-blister 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.

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 member states agreed that no further non-clinical studies are required.

With regard to reproduction toxicity, effects appear to be limited to high doses. A single study is mentioned in which teratogenic effects were observed in rabbits at doses 300-1500 µg/kg/day. These data however, have only been published in the form of an abstract in a journal that is not peer reviewed. No underlying data is available, and both the relevance and outcome are questionable. Furthermore, other rabbit studies that have been performed with doses of up to 1000 µg/kg/day (around 400-fold the human dose, based on body surface area), showed no teratogenicity. Overall, it can be concluded that misoprostol does not have teratogenic potential in animals.

Although misoprostol is a known active substance, the indication that is applied for in the current procedure has not been approved before. Therefore, substitution of products already on the market does not apply in this case.

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

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 overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Pharmacokinetics
After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. The drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid. Following a single oral dose of 400 µg oral misoprostol, the plasma misoprostol acid level increases rapidly and peaks at about 30 minutes, declines rapidly by 120 minutes and remains low thereafter.

There is a high variability of plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose over the range of 200-400 µg.

No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady-state was achieved within 2 days. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid.
After oral administration of radiolabelled misoprostol, about 73% of detected radioactivity is excreted in urine, and about 15% is excreted in the faeces. About 56% of total radioactivity is eliminated within 8 hours via urine.
Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of t½, C_{max}, and AUC compared to normal, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range. Misoprostol is metabolised by fatty acids-oxidizing systems, present in several organs of the human body.
After a single oral dose of misoprostol to nursing mothers, misoprostol acid was excreted in breast milk. The maximum concentration of misoprostol acid in expressed breast milk was achieved within 1 hour after dosing and was 7.6 pg/ml (% CV 37%) and 20.9 pg/ml (% CV 62%) after single 200 µg and 600 µg misoprostol administration, respectively. The misoprostol acid concentrations in breast milk declined to < 1 pg/ml at 5 hours post-dose.

Bioequivalence study
For this hybrid application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product MisoOne 400 µg (Exelgyn, France) is compared with the pharmacokinetic profile of the reference product Cytotec 200 µg (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 µg test or 2x 200 µg reference) of one of the two misoprostol formulations. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of seven 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	**$AUC_{0-\infty}$** 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	--	--

$AUC_{0-\infty}$ 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
**ln-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 µg and two tablets of Cytotec 200 µg 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).

Pharmacodynamics

The effect of misoprostol on uterine contractility has been studied by Gemzell-Danielsson et al., and by Aronsson et al. (Gemzell-Danielsson 1999; Aronsson 2004). An increase of uterine tonus is observed after a single oral dose of 400 µg misoprostol (Figure below) (Aronsson 2004; Norman 1991).

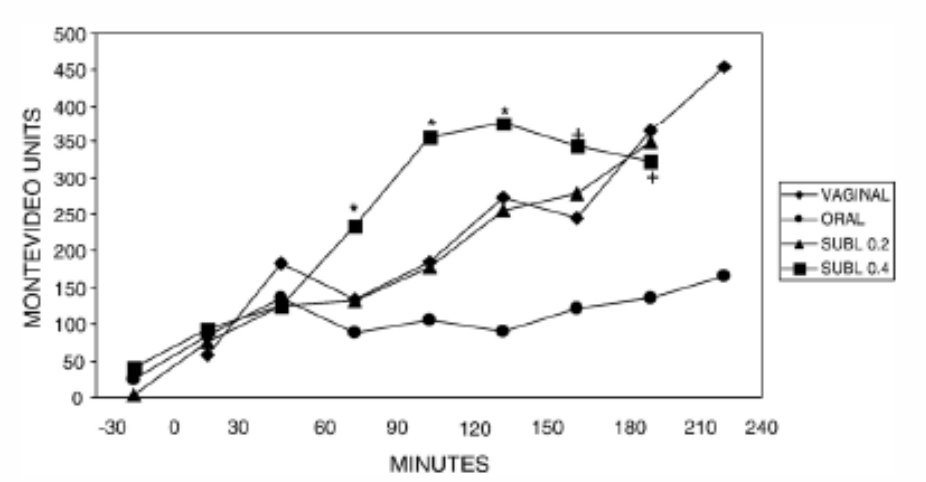

Figure 5: Uterine Activity was Measured in Montevideo Units (MU). The Treatment Groups were as Follows: Vaginal (0.4 mg), Oral (0.4 mg) and Sublingual (0.2 and 0.4 mg). Significant Differences Between the Means of the Sublingual (0.4 mg) and Oral group: *P<0.05; †pooled sublingual groups (0.2 and 0.4 mg) (Aronsson 2004).

The effect of vaginal administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration, i.e. an increase in uterine tonus. However, after 1-2 hours uterine contractions appear, and they last at least up to 4 hours after the vaginal administration of misoprostol (Gemzell-Danielsson 1999).

The mean time to increase in tonus is 8 minutes for oral administration of misoprostol, and 20 minutes for vaginal administration. The mean time to maximum tonus is also significantly shorter for oral misoprostol compared to vaginally administered misoprostol. One to two hours after administration of misoprostol the tonus begins to decrease. In the case of oral misoprostol, this is the end of activity. For vaginally administered misoprostol the tonus is slowly replaced by regular uterine contractions.

The studies on uterine contractility so far have shown that a sustained level, rather than a high serum level, is required for the development of regular uterine contractions. Studies have failed to define the threshold serum level for uterine contractility. As the sensitivity of the uterus to prostaglandins increases with gestation, the clinical effects or actions required for different indications of use also vary. For instance, stronger contractions are required for labour induction than for medical ToP. For medical ToP, the addition of mifepristone would certainly modify the action of misoprostol and lower the serum threshold level for uterine contractility (Tang 2007).

Clinical efficacy
Misoprostol is proposed to be indicated for:

- *Medical termination of developing intra-uterine pregnancy, in sequential use with a synthetic antiprogesterone (mifepristone [Mifegyne®]), up to 49 days of amenorrhea.*

Twenty-nine publications were obtained from literature describing the efficacy of mifepristone (any dose) in combination with oral misoprostol (any dose) for medical ToP in women with ≤63 days of amenorrhea.

Eight studies that report efficacy results on medical ToP with 600 mg mifepristone followed 48 hours later by 400 µg misoprostol in women with ≤49 days of amenorrhea, i.e. the exact regimen as proposed by Exelgyn are considered pivotal. Of these, two clinical studies, in which mifepristone is used in combination with misoprostol for medical ToP, full reports are included in this dossier. Those two clinical studies have been evaluated by the Authorities of countries where a MA was granted for mifepristone (Mifegyne®).

Eleven publications have been identified that describe ToP with mifepristone (any dose) and misoprostol doses other than 400 µg. In addition, 3 publications have been identified that are based on the data of a large U.S. study by Spitz et al. (Spitz et al., 1998), namely Jain et al (1999), Winikoff et al (1998) and Harper et al (2002).

Pivotal Efficacy Studies
Two studies were conducted by Peyron et al. to determine the efficacy of 600 mg mifepristone followed by a small dose of misoprostol for terminating early pregnancy. The aim of the first study was to investigate the efficacy and tolerance of mifepristone (600 mg in a single dose) in combination with misoprostol (400 µg 36 to 48 hours later) in the ToP with ≤49 days of amenorrhea (Peyron 1993), the dose regimen which is also part of this application. This study was part of the Mifegyne® MA file which was evaluated by the Authorities of the countries where this drug is approved.
It is an open, multicentre, non-comparative study, conducted in accordance with French law on abortions. This report covers 1,286 women, representing all the cases in the study. The therapeutic regimen was as follows: after the statutory one week period for reflection and signature of a consent form, the patients took 600 mg of mifepristone in the presence of the investigator. They returned 36 to 48 hours later for administration of misoprostol: 400 µg, again in the presence of the investigator, and remained in the centre for 4 hours for monitoring. The efficacy of the method was assessed at a follow-up visit 8 to 15 days after administration of mifepristone. The haemoglobin level was measured at the time of inclusion and at the follow-up visit. For the 1.208 cases evaluable for efficacy the results revealed a success rate (i.e. terminated pregnancies with complete expulsion) of 95.36% (95% CI: 94%-96.5%). Failures (4.64%) were divided into on-going pregnancies requiring aspiration (1.49%), ToP with incomplete expulsion followed by a supplementary surgical procedure (2.81%) and haemorrhage requiring a haemostatic endo-uterine procedure (0.33%).
The results of this study confirmed the good efficacy and tolerance of the combination of mifepristone and misoprostol in the ToP of ≤49 days of amenorrhea.

A summary of the other studies is also presented in the overview submitted with this application, including those studies which used other dosages, for ≥49 days of amenorrhoea, and comparison with vaginal administration of Cytotec oral tablets.

Clinical safety
Dose regimen in reducing the risk of NSAID-induced gastric ulcers (200 µg 4 times daily)
Misoprostol has been marketed in the EU as Cytotec and is available in tablets of 100 µg and 200 µg. Generics are also available. The recommended adult oral dose for the marketed indication i.e. reducing the risk of NSAID-induced gastric ulcers is 200 µg 4 times daily with food. If this dose cannot be tolerated, a dose of 100 µg can be used. Since misoprostol has been marketed for a number of years as Cytotec, the safety and tolerability after oral administration of this drug are well established. The most common side effects observed after treatment with misoprostol are gastrointestinal disorders (nausea, vomiting, diarrhoea), abdominal pain/uterine cramps, headache, fever, and chills (Cytotec Pfizer warning (2009) U.S., Searle & Co.).

Misoprostol in combination with mifepristone used as an abortifacient (400 µg misoprostol single dose after pretreatment with mifepristone 600 mg)
Twenty-eight publications describe the safety of the use of mifepristone and misoprostol for medical ToP. These publications involve > 15,000 women world-wide with ≤63 days of amenorrhea treated with the combination of mifepristone and oral misoprostol for medical ToP.
All were women of childbearing potential and many races have been studied (including Caucasian and Asian women). Approximately 8,700 women were treated with the combination of 600 mg mifepristone and 400 µg misoprostol, and approximately 6,300 women were treated with other dosing regimens.

Common and uncommon side effects
The most frequently observed side effects observed after the administration of mifepristone and misoprostol for medical ToP were (moderate) uterine cramping and/or abdominal pain, gastrointestinal symptoms (especially nausea, vomiting, and diarrhoea), headache, dizziness, and back pain. These side effects were generally mild and did not require analgesia. The incidence and severity of these side effects increase with increasing duration of pregnancy. Serious side effects such as haemorrhage and infection were rarely observed, and included an incidence of excessive bleeding requiring surgical intervention (Winikoff 1997).
Uterine bleeding, painful uterine contractions and/or cramps similar to labour or menstrual cramps are all expected consequences of medical ToP. After mifepristone administration and prior to misoprostol administration, abdominal pain or discomfort, nausea, tiredness, and breast pain were frequently reported. In many women these symptoms, which are often associated with pregnancy, were present before administration of mifepristone, being subsequently intensified by the pharmacologic action of the antiprogesterone compound.

Special Safety Concerns
Although good tolerability, safety, and efficacy are reported for medical ToP with the combination of mifepristone and misoprostol, some issues have been identified that require special attention. These issues are described in the following paragraphs and are often associated with the off-label use of misoprostol i.e. different dose, different route of administration, or different dosing interval than described in the Mifegyne® SmPC.

Safety and Tolerability of Alternative Administration Routes
Despite the license for oral use only, misoprostol is also widely used via alternative, unlicensed, administration routes (per vaginam, bucally, or sublingual). The higher bioavailability observed after vaginal or sublingual administration may lead to a higher efficacy. Indeed, vaginal administration of misoprostol has shown a higher rate of success in medical ToP, but the risk of fatal infections has led the CHMP and EMA to strongly advise against this method of administration.
Other side effects may also increase when alternative administration routes are used. This side effect increase is detailed in the Risk Management Plan (RMP) for misoprostol. The pelvic pain intensity and duration are also linked to the route of administration of the oral misoprostol tablets. Aubeny et al (Aubeny 2000) compared the efficacy and tolerance of mifepristone and misoprostol administered orally or vaginally for the termination of pregnancy up to 49 days of gestation. Administration of misoprostol by either the sublingual or buccal route have shown a lower tolerability for the women in terms of pain, diarrhea, nausea, vomiting, fever and chills.

Reports of Congenital Malformations Following Misoprostol Administration
Although misoprostol has no teratogenic actions in pregnant rats and mice, in humans the teratogenic risk of exposure to mifepristone and misoprostol for the foetus remains to be quantified.
Prospective studies investigating relationships between misoprostol and Moebius syndrome or other birth defects have yielded controversial results. Schüler et al. (1999) and Schönhofer (1991) did not find any teratogenic effects in 86 pregnant women exposed to misoprostol in comparison to 86 pregnant women without misoprostol exposure. In contrast, several studies report on an increased risk of congenital malformations after misoprostol use. Most of these studies involved illegal use of the drug, and most reports originate in Brazil, where abortion is not legalized and misoprostol alone is often used as an abortifacient. According to controlled clinical trials, medical ToP using misoprostol alone can lead to failed

abortions in over 10% of cases (Goldberg 2001). As the single use of misoprostol is considerably less effective than combinations with e.g. mifepristone, this treatment is not recommended for first trimester abortion.
When abortion fails, the use of misoprostol has been associated with the occurrence of teratogenic effects such as amiotic band syndrome (terminal limb defects) and Moebius syndrome (a rare disease characterised by congenital facial paralysis and abducens palsey) in infants whose mothers took misoprostol in an attempt at abortion.

Pharmacovigilance system
The member states consider that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the applicant 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 activities (Routine or additional)	Proposed risk minimisation 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	Pharmacovigilance Routine 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	Pharmacovigilance Routine Event of interest for signal detection	SmPC PIL Educational Material kit

In the first and second assessment round several questions were raised on the RMP. These were adequately answered. With regard to the AMAYA study, it is clarified in the RMP that the results obtained in this study are an extrapolation (and not the actual data) for MisoOne, because Cytotec is the product that was investigated. Based on demonstrated bioequivalence of MisoOne with Cytotec, the safety and the efficacy profile collected for Cytotec in this study can be extrapolated to MisoOne. In the same line, the sample size of the AMAYA study is calculated based on the expected failure rate of Cytotec, which is considered adequate for MisoOne.
The educational materials are acceptable. Final content, lay-out, target audience, and distribution method should be agreed with individual national competent authorities at a national level.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is acceptable and has been adapted in accordance with the comments raised by the member states.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. There was a pilot test phase with 3 subjects, followed by 2 test rounds with 10 subjects each. The test persons were female volunteers aged from 18 to 51 years with most of them between the ages of 20 and 35 years. They were all native English speakers. Educational levels correspond with the inclusion criteria set in the protocol.
The original leaflet was first refined before the key points of information were defined. The key points are intended to reflect the safety issues identified as important to the safe and proper use of the medicine.
The test included 15 questions on the text of the leaflet and 1 open question regarding general impressions of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections.
Scoring was separately analysed for the two test rounds. No amendments were proposed between the two rounds. The results 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.
The package leaflet passed the user test successfully.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

MisoOne 400 micrograms, tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Cytotec 200 µg 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.

The therapeutic indication of MisoOne 400 micrograms differs from the innovator, as well as the dose. 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.* In France 200 µg misoprostol tablets are approved for this indication.
The MAH submitted satisfactory non-clinical and clinical overviews to support use in medical ToP.

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 Mifegyne. The SmPC, package leaflet and labelling are in the agreed templates.

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, have granted a marketing authorisation. The decentralised procedure was finished on 29 October 2012. MisoOne 400 micrograms, tablets was authorised in the Netherlands on 4 December 2012.

The date for the first renewal will be: April 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to initiate a stability study for batches of finished product manufactured with 6 months old misoprostol dispersion.

List of abbreviations

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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
ToP	Termination of Pregnancy
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
Change in product name	NL/H/2355/ 001/IB/001	IB	26-02-2013	28-03-2013	Approval	N
Change in the invented name of the medicinal product in Austria, Bulgaria, Czech Republic, Germany, Estonia, Latvia, Portugal, Romania, Sweden and Slovenia.	NL/H/2355/ 001/IB/002	IB	29-7-2013	30-10-2013	Approval	N
Extension shelf life OPA-Alu-PVC/Alu blister: 6 months -> 18 months.	NL/H/2355/ 001/IB/003	IB	27-8-2013	26-9-2013	Approval	N
Introduction of a new summary Pharmacovigilance System Master File.	NL/H/2355/ 001/IA/004	IA	8-1-2014	7-2-2014	Approval	N
Extension of the shelf-life of the finished product on the basis of new data available on industrial batches	NL/H/2355/ 001/IB/005	IB	13-1-2014	19-3-2014	Approval	N
Addition of finished product manufacturer and consequential changes	NL/H/2355/IB/006/G	IB	9-9-2014	16-11-2014	Approval	N
Addition of a manufacturer responsible batch release, including batch control/testing.	NL/H/2355/ 001/IA/007	IA	28-1-2015	27-2-2015	Approval	N
Addition of a batch control testing site	NL/H/2355/ 001/IA/008	IA	10-2-2015	12-3-2015	Approval	N
Repeat use procedure to register the product in Greece and Croatia	NL/H/2355/ 001/E/001	E	10-11-2015	8-2-2016	Approval	N
	NL/H/2355/ 001/P/001	P				
Renewal of the Marketing Authorisation	NL/H/2355/ 001/R/001	R	12-1-2018	15-6-2018	Approval	Y
Deletion of a manufacturing site Addition of a primary packaging site Addition of a secondary packaging site Change to batch release arrangements and quality control testing of the finished product - including batch control/testing Change in immediate packaging of the finished product - qualitative and quantitative composition	NL/H/2355/IA/009/G	IA	28-7-2017	25-8-2017	Approval	N
Implementation of wording agreed by the competent authority	NL/H/2355/ 001/IA/010	IA	5-6-2018	4-7-2018	Approval	N
Addition of a new indication: Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester.	NL/H/2355/ 001/II/011	II	21-9-2018	19-6-2019	Approval	Y
The current tablet is a large tablet (11 mm diameter, 4.4 mm thickness). The aim of this variation is to get a break line on each side of the tablet of MisoOne / Topogyne / Mispregnol to facilitate its swallowing. Thus the tablet could be divided into equal doses. This led to a change in the appearance and the thickness of the tablets. An addition of a test	NL/H/2355/IB/012/G	IB	12-2-2019	25-4-2019	Approval	N

has been made: subdivision of tablet following the Ph.Eur. 0478 with an addition of a new specification parameter and of a test procedure for the finished product.						
Deletion of a batch control testing & batch release site	NL/H/2355/ 001/IA/013	IA	7-2-2019	5-3-2019	Approval	N
Implement the outcome of the PRAC Assessment Report on the PSUR(s) for mifepristone / misoprostol, following the wording proposed on the PSUSA_00010378/201705.	NL/H/2355/ 001/IA/014	IA	7-2-2019	2-4-2019	Approval	N
Repeat use procedure to register the product in Cyprus and Ireland	NL/H/2355/ 001/E/002	E	13-9-2019	13-9-2019	Approval	N

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ANNEX I – Renewal of the marketing authorisation (variation NL/H/2355/001/R/001)

I RECOMMENDATION

Based on the review of the data submitted for the renewal application, the member states consider that the benefit/risk balance of MisoOne 400 µg tablets (NL/H/2355/001/R/001) is positive. The member states are also of the opinion that the renewal can be granted with unlimited validity.

II EXECUTIVE SUMARY

II.1 Introduction

MisoOne contains the active substance misoprostol. Misoprostol is a synthetic analogue of prostaglandin E1 used in adults in combination with mifepristone for the medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days post-LMP (Last Menstrual Period), as a single 400 µg oral dose.

Misoprostol was registered through a decentralised procedure (NL/H/2355/001/DC) involving 21 countries which was positively ended on 30 October 2012. The following countries were involved: AT, BE, DK, FR, FI, NO, SE, DE, NL, ES, LU, EE, LV, PT, RO, IT, UK, CZ, SI, SK, BG. In parallel to the 400 µg oral tablet registration, a 200 µg tablet dose is also registered in the Netherlands only (Misoprostol Exelgyn 200 µg tablets) through a National Procedure (2 July 2013).

For this renewal procedure, the MAH submitted an addendum to clinical overview (dated July 2016), covering the period 30 October 2012 to 31 May 2016.

II.2 GMP compliance statements

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the Community, copies are accepted of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance, a statement is provided from the manufacturers responsible for manufacture of the finished product and batch release situated in the EU.

Risk Management Plan
An updated EU-RMP has been submitted for MisoOne during this renewal procedure. The RMP (v5.0) is dated 28 July 2016 and is discussed in the clinical paragraph.

III SCIENTIFIC DISCUSSION

III.1 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (see CMDh website http://www.hma.eu/95.html) a quality expert statement has been submitted, confirming:

- That the product is in compliance with Article 23 of Directive 2001/83/EC which obliges the MAH "…. to take account of technical and scientific progress and introduce any changes…".
- That all changes relating to the quality of the product have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished product with the qualitative and quantitative composition have been provided.

III.2 Non-clinical aspects

No non-clinical data, either from published studies or from MAH-sponsored non-clinical studies were gathered during the interval.

III.3 Clinical aspects

III.2.1 Clinical efficacy
There was no new information on efficacy and effectiveness during the reporting interval.

III.2.2 Clinical safety
History of pharmacovigilance inspections
One pharmacovigilance inspection took place in the reporting period. All corrective and preventive actions (CAPAs) were accepted and closed and currently there are no open critical or major findings. Results of the inspection had no impact on the benefit/risk balance.

Actions taken in the reporting interval for safety reasons
No action for safety reasons was initiated for the product.

Significant changes to the summary of product characteristics
The reference safety information is the EU-SmPC, last updated in October 2014. It was approved upon completion of the decentralized procedure for misoprostol obtained in October 2012.

Estimated exposure and use patterns
Cumulative subject exposure in clinical trials
No MAH-sponsored interventional clinical trial was conducted during the reporting period.

Cumulative subject exposure in non-interventional clinical trials

- 1,587 patients were included by 47 centres in the observational study Amaya (objective: describe the real-life efficacy and tolerance of drugs used in chemical medical termination of pregnancies (MToPs)).
- 322 patients were included by 17 centres in the non-interventional longitudinal BETINA study ('feasibility of a self-performed urinary test for the follow-up on medical abortion').
- 542 patients were included in the non-interventional longitudinal MYA study ('Epidemiological study on cervical preparation methods before elective surgical abortion currently used in centres') was initiated in France. The final study report is ongoing.
- 881 patients were included in the non-interventional prospective, multicentre, longitudinal study RYMMa entitled 'Efficacy of mifepristone – prostaglandin analogue combination in medical termination of pregnancy beyond 7 weeks of amenorrhea'.

Cumulative patient exposure from marketing experience
In total, up to 31 May 2016, it is estimated that total number of patients treated with MisoOne is between 101,932 patients (average dose of 533 µg) and 135,824 patients (average dose of 400 µg).

Post-approval use in special populations
No relevant new safety information on misoprostol use in special populations became available during the period covered by this report.

Off-label use
- Early pregnancy failure: Early pregnancy failure is an unapproved indication for MisoOne. No significant safety findings became available during the period covered by this report.
- Incomplete miscarriage and incomplete induced abortion: Incomplete miscarriage and incomplete induced abortion are unapproved indications for MisoOne. No significant safety findings became available during the period covered by this report.
- Cervix dilation prior to surgical abortion: No relevant new significant safety findings were received during the period covered by this report.
- Pregnancy termination for medical reasons beyond the first trimester: Pregnancy termination for medical reasons beyond the first trimester is an unapproved indication for MisoOne. No relevant new information was received during the period covered by this report.

Overdose
No case of massive overdose of misoprostol was received during the reporting interval.

Data in summary tabulations
Cumulative summary tabulations of serious AEs from clinical trials
There were no serious AEs during the reference period from MAH-sponsored clinical trials.

Cumulative and interval unsponsored clinical trials summary tabulations
The MAH provided a cumulative and interval summary tabulation of serious and non-serious adverse reactions from marketed experience. No new safety information was identified.

Significant safety and efficacy findings from clinical trials and non-interventional studies
Interventional clinical trials
No interventional clinical trials were completed during the reporting period.

Non-interventional clinical trials
Amaya
The observational study Amaya, whose objective was to describe the real-life efficacy and tolerance of drugs used in chemical MToPs, was conducted between 14 September 2011 (first consultation with the first patient) and 15 March 2012 (follow-up visit with the last patient). The final report is available. 1,587 patients were included by 47 centres.

In this study of 1585 women who had received a chemical MToP, there was a similar success rate of 94.4%, (95% CI (93.12; 95.57)) regardless of the treatment protocol used. Bleeding (98.2%), abdominal pain (82.2%) and episodes of diarrhoea (34.3%) were more frequent after taking the prostaglandin. Nausea (63.1%), vomiting (36.5%) and antibiotic use (11.1%) were more often reported by patients whose term was more than 49 days. Headache (38.1%) was reported more often after taking the mifepristone and by patients whose term was more than 49 days. Overall, this study showed a real-life high success rate for chemical MToP that matches the plethora of data in the literature. Regardless of the protocol used, this approach is effective and well tolerated, and satisfied the majority of patients (90.4%).

Betina
This study assessed, in real life conditions, the benefit of a urinary semi-quantitative test (hCG Duo 5-1000) in the follow-up of medical abortion by analysing the agreement between qualitative results from the urinary test and quantitative values from the β-hCG blood measurement and secondarily the feasibility and acceptability of the urinary test. The final report was provided together with PSUR #3. The rationale of

this study was based on the observation that not all patients attend the follow-up visit after MToP. Thus, the existence of a simple method to check the termination of pregnancy, such as semi-quantitative urine β-hCG tests, would demonstrate the result of the MToP and educate the patients before a medical confirmation. This urinary test is not intended to replace the follow-up visit.

A total of 322 patients seeking for medical abortion were included between the 23 May 2013 (date of the first consultation of the first patient) and the 29 November 2013 (date of the follow-up visit of the last patient) by 17 centres in France. The successful abortion rate was calculated to be 93.6% (with inclusion of secondary success after additional intake of Cytotec) and consistent with the literature data.
A total of 31 cases of pharmacovigilance (all serious) were received from the BETINA study. These cases consisted in 24 cases of incomplete retention and seven cases of complete retention of products of conception. The failures included two viable pregnancies which were terminated by vacuum aspiration. Of the 280 patients of the efficacy study, one patient (0.4%), between 36 and 42 days post-LMP at the time of drug intake, developed uterine haemorrhage associated with retained products of conception requiring secondary surgical procedure. During the follow-up visit, the result of the MToP was checked using a measurement of β-hCG in 95.1% of patients and an ultrasound in 50%. The semi-quantitative urine β-hCG test was performed in due time for 76% of patients accordingly to physicians advices. The agreement between the urine and blood results was found to be very good (94.5% when the tests were performed the same day ±1 day).
In conclusion, the semi-quantitative urine β-hCG test was mostly well accepted by the patients. A majority of patients found that the use of the urinary test to check the results of the MToP by themselves was reassuring or satisfactory. There was no decrease in the attendance rate to the follow-up visit, which remains essential to check the outcome of the MToP.

RYMMa
During the reference period the non-interventional prospective, multicenter, longitudinal study RYMMa untitled “Efficacy of mifepristone – prostaglandin analogue combination in medical termination of pregnancy beyond 7 weeks of amenorrhea.” is conducted in France, among a representative sample of public and/or private birth control centers. The aim of the study is to assess in real-life settings the efficacy of the mifepristone-600 mg/prostaglandin analogue combination in women asking for MToP beyond 7 weeks of amenorrhea. This study started in France in December 2015. The patient enrollment was closed for all centers in May 2016; the total number of patient included in this study is 881 patients.
At the data lock point of this report, a total of 83 cases (66 serious, 17 non-serious) reporting AEs related to the administration of mifepristone had been received from the study. Among these 83 cases, there were 90 AEs (67 serious not fatal, 23 non-serious) and 137 codings for special situations and off-label use. None of these 67 serious AEs were deemed unexpected for Mifegyne (EU SmPC). Most of 90 AEs fell into the following MedDRA SOCs, in order of decreasing frequency: Injury, poisoning and procedural complications (64 AEs), Gastrointestinal disorders (13 AEs), Reproductive system and breast disorders (7 AEs). These 67 serious AEs divided into 49 AEs of ‘Abortion induced incomplete’, 15 AEs of ‘Induced abortion failed’ and 2 AEs of ‘Metrorrhagia’ (MedDRA PTs v.18.1).
Among these 83 cases, 68 cases were associated with at least one off-label use (EU SmPC), involving mifepristone in 6 cases (buccal route: 3 cases, intake after 63 days post-LMP: 3 cases) and misoprostol in 68 cases. In 38 cases, misoprostol was combined with mifepristone for pregnancy termination between 50 and 63 days post-LMP and in 3 cases mifepristone and misoprostol were administered after 63 days post-LMP for MToP.

In total, no new significant safety information for misoprostol became available from this study.

Literature
The MAH provided a literature overview focused on information regarding the benefit/risk of the combined use of mifepristone and misoprostol. No new safety information was identified from these publications. The following topics were included in the literature review:

Medical termination of developing intra-uterine pregnancy

The provision of safe abortion services to women who need them has the potential to drastically reduce or eliminate maternal deaths due to unsafe abortion (Kapp 2013[1], WHO 2012[2]). Both medical and surgical methods of abortion are available. Medical abortions have the advantage of being able to be prescribed in a physician's office, as long as the gestational age of the pregnancy can be accurately diagnosed. Reasons for not choosing medical abortion include the requirement for several visits, lack of immediacy, dosing schedule, and swallowing pills. Some women expressed fear of toxicity, pain, or side effects of the medication, anxiety over the start of the process, and fear of potential psychological sequelae (Bryant 2014[3], Costescu 2016[4], Fiala 2014[5]).

Options and dose regimens for medical abortion

Although several options of medication are available, using the antiprogesterone mifepristone and the prostaglandin E1 analog misoprostol is mentioned by many references as the golden standard and the most commonly used for medical abortion (WHO 2012[2], Raymond 2013[6], Bryant 2014, Saurel-Cubizolles 2015[7]). Medical abortion with combined mifepristone and misoprostol has been established as a highly effective, safe, and acceptable method for medical termination of pregnancy for the past 25 years (Oppegaard 2015[8]). Serious complications requiring hospitalization or transfusion occurred in less than 0.4% of patients (WHO 2012[2], Kapp 2013[1]).

With regard to misoprostol use by vaginal, buccal, sublingual or oral routes, a retrospective analysis assessed the rates of serious infections, and the rate of serious infection after medical abortion declined by 93% after the change from vaginal to buccal administration, combined with routine antibiotic therapy (Fjerstad 2009[9]). No new information which could change these positions has become available recently.

Misoprostol given orally at a dose of 400 µg is to be restricted to pregnancies up to 7 weeks' (49 days') gestation, given a higher failure rate when given orally as pregnancy progresses (WHO 2012[2], Dickinson 2014[10]).

Raymond et al (2013)[11] performed a systematic review of 87 trials that collectively included 120 groups of women treated with a regimen of interest. Across all trials, 119 evaluable subjects (0.3%) were hospitalized, and 0.1% received blood transfusions (Raymond 2013[11], Raymond 2015[12]).

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[1] Kapp N, Whyte P, Tang J, Jackson E, Brahmi D. A review of evidence for safe abortion care. Contraception. 2013 Sep;88(3):350-63.

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[3] Bryant AG, Narasimhan S, Bryant-Comstock K, Levi EE. Crisis pregnancy center websites: Information, misinformation and disinformation. Contraception. 2014 Dec;90(6):601-5.

[4] Costescu D, Guilbert E, Bernardin J, Black A, Dunn S, Fitzsimmons B, et al1. Medical Abortion. J Obstet Gynaecol Can. 2016 Apr;38(4):366-89.

[5] Fiala C, Cameron S, Bombas T, Parachini M, Saya L, Gemzell-Danielsson K. Pain during medical abortion, the impact of the regimen: a neglected issue? A review. Eur J Contracept Reprod Health Care. 2014 Dec;19(6):404-19.

[6] Raymond EG, Shannon C, Weaver MA, Winikoff B. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 87 (2013) 26–37.

[7] Saurel-Cubizolles MJ, Opatowski M, David P, Bardy F, Dunbavand A. Pain during medical abortion: a multicenter study in France. European Journal of Obstetrics & Gynecology and Reproductive Biology 194 (2015) 212–217

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[11] Raymond EG, Shannon C, Weaver MA, Winikoff B. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 87 (2013) 26–37.

[12] Raymond EG, Grossman D, Wiebe E, Winikoff B. Reaching women where they are: eliminating the initial in-person medical abortion visit. Contraception 92 (2015) 190–193.

For service delivery and patient convenience, a single dose of mifepristone is recommended. The 600 mg and 200 mg mifepristone dose differ in safety level with a higher greater pain level for the 200 than 600 mg mifepristone (Saurel-Cubizolles 2015)[13].

A recent clinical study with oral misoprostol in Ukraine is reported by Raghavan et al. (2013)[14], results of two clinical trials. Women were given 200 mg mifepristone followed after 48 hours by 400 µg oral misoprostol (study one) and mifepristone followed after 24 hours by 400 µg sublingual misoprostol (study two). The oral and sublingual regimens worked very well. In combination with mifepristone, 400 µg of oral misoprostol is very efficacious to 56 days' LMP.

Safety aspects

- Failed abortion: The most serious complication of medical abortion, an unidentified ongoing pregnancy, was found in 1% of the 45,000 women (WHO 2012[2]). Rates vary according to the regimen used and gestational age. Costescu (2016)[15] reports on average, approximately 3% to 5% of women having mifepristone-based medical abortion have a subsequent aspiration. Symptoms include unexpected heavy or prolonged bleeding and cramping, or, in the case of a no expelled pregnancy, failure to have expected bleeding (Costescu 2016[15]).
- Misoprostol tablet instability due to blister damage: A study by Berard et al (2014)[16] showed that exposure of Cytotec tablets to 'typical' European levels of air and humidity results in significant time-dependent changes in physical and biological composition. Cytotec does not have the indication termination of pregnancy, it is indicated for stomach protection.
- Abdominal pain: A review by Fiala et al. (2014)[17] shows that, pain experienced during medical abortion is not systematically assessed in clinical trials and that, consequently, little information on this aspect is on record.
  Saurel-Cubizolles (2015)[13] report that pain was greater with 200 mg than 600 mg mifepristone: 33% of women reported a pain level of equal or larger than 8 on day 3 with 200 mg as compared with 16% with 600 mg. These findings emphasize the need to improve analgesic strategies and invite to opt for a protocol of 600 mg instead of 200 mg mifepristone.
- Septic shock: The frequency of infections among women treated with mifepristone and oral misoprostol regimens was much lower (0.21%, N=13.497) compared to vaginal administration (Art 31 referral 2007), the vast majority of cases after oral administration were diagnosed as endometritis. Two cases of toxic/septic shock were reported in literature during the reporting period 2012 to 2016. One was after vaginal use of misoprostol or gemeprost. One was after oral use of misoprostol after clandestine abortion by misoprostol self-administration. The current data therefore confirm the previous findings on the occurrence of infections and septic shock after medical abortion and oral mifepristone/misoprostol administered under supervision in line with the treatment protocol of the MToP service clinic is at very low risk of septic shock. Cumulative date on septic shock and toxic shock syndrome showed a total of 16 reports mainly issued from literature. Thirteen of these reports were fatal and in 14 cases, Misoprostol was administered vaginally.
- Serious complications: Serious complications of medical abortion requiring hospitalization or blood transfusion were rare, occurring in 0.4% of women (WHO 2012)[2].

[13] Saurel-Cubizolles MJ, Opatowski M, David P, Bardy F, Dunbavand A. Pain during medical abortion: a multicenter study in France. European Journal of Obstetrics & Gynecology and Reproductive Biology 194 (2015) 212–217

[14] Raghavan S1, Maistruk G, Shochet T, Bannikov V, Posohova S, Zhuk S, Lishchuk V, Winikoff B. Efficacy and acceptability of early mifepristone-misoprostol medical abortion in Ukraine: results of two clinical trials.Eur J Contracept Reprod Health Care. 2013 Apr;18(2):112-9.

[15] Costescu D, Guilbert E, Bernardin J, Black A, Dunn S, Fitzsimmons B, et al1. Medical Abortion. J Obstet Gynaecol Can. 2016 Apr;38(4):366-89.

[16] Berard V, Fiala C, Cameron S, Bombas T, Parachini M, Gramzellz-Danielson K. Instability of misoprostol tablets stored outside the blister, apotential serious concern for clinical outcome in medical abortion. PLOS ONE December 15, 2014.

[17] Fiala C, Cameron S, Bombas T, Parachini M, Saya L, Gemzell-Danielsson K. Pain during medical abortion, the impact of the regimen: a neglected issue? A review. Eur J Contracept Reprod Health Care. 2014 Dec;19(6):404-19.

Methods to simplify medical abortion

Medical abortion protocols require that each patient must present in person to a clinical facility to obtain the service. At this moment, there is a global trend in developing approaches to allow women to obtain medical abortion with less or even without a clinic visit.

- Misoprostol at home: In most countries where early medical ToP is legal, women are able to administer the second part of this treatment regimen (misoprostol) at home (Cameron 2015)[18]. Raymond et al. (2013, 2015)[11,12] found no evidence that allowing women to take the misoprostol at home increased the rates of abortion failure or serious complications. The acceptability of at home administration of misoprostol is supported by several studies. In the Ukraine studies using oral misoprostol administration, it was found that women could safely administer their own oral misoprostol in the privacy of their own homes (Raghavan 2013)[14]. WHO guidelines (2012)[2] endorse less visits: at home use of misoprostol is a safe option for women. Most women are likely to require medication for cramping pain during this period of time.
- Initial visit: Even for women who live near an abortion facility, the visit may be expensive and inconvenient. Raymond et al. (2015)[12] argue that many elements of the initial visit do not require a clinical venue and can be solved or taken care of in another way, thereby eliminating the need for this initial visit.
- Mifepristone at home: Giving women mifepristone to take at home has the potential to make medical abortion more acceptable and accessible (Chong 2015)[19]. Success and complication rates were not different between home users and clinic users.
- Follow-up visit: Another most studied method to reduce visits to the clinic is that of follow-up to exclude ongoing pregnancy is that of a telephone follow-up from the ToP provider combined with a self-performed pregnancy test conducted by the woman herself at home (Cameron 2015)[18]. With decades of clinical experience with medical ToP, many ways to simplify its follow-up, including serum and urine hCG testing, have been explored (Hassoun 2016)[20]. Further development in order to provide midstream urinary tests applying only one detection threshold could be better adapted to the detection of ongoing pregnancies in medical TOP (Hassoun 2016)[20].
  No clinical follow-up is becoming increasingly common and will be seen even more frequently when medical abortion becomes the standard method (Oppegaard 2015)[8]. Follow-up traditionally has involved a routine clinic visit for ultrasound. Reliance on ultrasound is costly and requires highly skilled staff, and for some services, the volume of repeat appointments may limit the number of new referrals that can be seen (Cameron 2015)[18].
- Over-the-counter: The pathway for women requesting an early medical ToP who are certain of their decision could consist of a single clinic visit (Cameron 2015)[18]. Taking a step even further, a discussion on complete self-administration and over–the–counter provision is ongoing on global level. However, it is likely that in certain areas in the world the expanded availability of abortion pills over the counter reduces maternal morbidity and mortality by offering a safer alternative than invasive or violent methods (Frye 2015)[21].

[18] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 91 (2015) 6–11.
[19] Chong E, Frye LJ, Castle J, Dean G, Kuehl L.Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the U.S. Contraception 92 (2015) 215–219
[20] Hassoun D, Perin I, Hien H, Demars HH Feasibility of self-performed urine pregnancy testing for follow-up after medical abortion. European Journal of Obstetrics & Gynecology and Reproductive Biology 197 (2016) 174–178.
[21] Frye LJ, Winikoff B. Comment on “Is It Safe to Provide Abortion Pills Over The Counter? A Study on Outcome Following Self- Medication with Abortion Pills. Journal of Clinical and Diagnostic Research. 2015 Aug, Vol-9(8): QL01-QL02.

Risk Evaluation
With this renewal application, the MAH included RMP version 5.0 (dated 28 July 2016). No update to the RMP is needed.

The following risks are included in the EU-RMP for misoprostol 400 µg tablet:

Summary of safety concerns	
Important identified risks	Teratogenicity on ongoing pregnancy Toxic and septic shock Uterine haemorrhage Abdominopelvic pain
Important potential risks	Misuse Cardiovascular ischemic disorders Uterine rupture
Missing information	Patients with renal impairment Patients with hepatic impairment

The MAH provided a summary overview of the EU proposed risk minimisation activities for misoprostol. Additional risk minimisation activities are in place for this medicinal product. Educational materials to communicate on appropriate usage of misoprostol for healthcare professionals and for patients (brochure and safety card) are in place for the following safety concerns: misuse, teratogenicity, toxic and septic shock, uterine haemorrhage, abdominopelvic pain, and cardiovascular disorders.

IV OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

During the reporting period, no new clinical and pre-clinical data became available which changes or results in a new benefit/risk evaluation. The MAH considers that the benefit-risk balance for misoprostol remains positive in the indication registered (medical termination of intra-uterine developing pregnancy in sequential use with mifepristone up to 49 days of amenorrhea). Important identified and potential risks for misoprostol continue to be monitored through routine pharmacovigilance activities.

In view of the efficacy and safety data reported in the literature during the reporting period, it is considered that there are no new specific areas that would require changes in the SmPC, and no update to the EU-RMP is needed.

The RMS is of the opinion that the renewal can be granted with unlimited validity.

ANNEX II – Extension of the indication (variation NL/H/2355/001/II/011)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, it is considered that the type 2 variation to extend the indication for MisoOne with the treatment of "Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester", is approvable.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

MisoOne contains misoprostol and is a hybrid registration (article 10(3) of Directive 2001/83/EC) with reference product Cytotec 400 microgram oral tablets. MisoOne is approved in the European Union on 29 October 2012 for the indication: *"Medical termination of developing intra-uterine pregnancy, in sequential use with a synthetic antiprogesterone (mifepristone [Mifegyne]), up to 49 days of amenorrhea".*

The current Type II variation concerns an extension of the indication with:
"Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester."

Proposed dose recommendation
Misoprostol is taken as a single 400 microgram oral dose 3 to 4 hours before surgical operation.
Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

The extension is supported by a clinical overview including an analysis of the efficacy and safety data and the rationale for extending the use of misoprostol for cervical preparation before surgical abortion during first trimester (SToP).

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

III.2.1 Environmental Risk Assessment
A final conclusion on potential risk of MisoOne to the environment cannot be drawn as the MAH did not provide any ERA studies in this procedure.

III.3 Clinical aspects

III.3.1 Pharmacokinetics
Pharmacokinetics of misoprostol following single oral route administration are well characterised and summarised in the current product information.

Bridging data

Twelve articles were presented to support the efficacy and safety of MisoOne in the requested indication. In two of these articles, Cytotec was stated specifically as the misoprostol product used in the studies. In the other eight articles (four studies were performed in Hong Kong, two in New Zealand, one in the USA and one in French West Indies), the misoprostol products used were not stated. Based on the search on data published in the local Medicine Agency database done by the MAH, Cytotec was the only registered misoprostol drug (single active ingredient) in the countries where the studies were conducted. So the MAH assumed that Cytotec was the product used in these eight studies. This can not be completely confirmed but based on the current available information (e.g. qualitative composition, among others) it is most likely that Cytotec tablets were used in these studies. Hence, this was agreed. In one article, two misoprostol tablets (Cytotec and Gymiso) were used in the study. According to the MAH, Gymiso was shown to be bioequivalent with Cytotec previously (TGA report October 2012, see link https://www.tga.gov.au/sites/default/files/auspar-misoprostol-121002.pdf). In one article, the misoprostol product used in the study could not be identified.

Overall, the Cytotec tablet can be considered as the misoprostol product used in about 90% (11 out of the 12 studies) of the supporting literature. Considering that Cytotec and MisoOne are bioequivalent, the data bridging the misoprostol products used in the published literature to MisoOne are considered sufficient. The composition and bioavailability of MisoOne and misoprostol products used in the literature are comparable to support the new indication for MisoOne.

III.3.2 Pharmacodynamics

The uterine cervix is essentially connective tissue organ. Smooth muscle cells account for less than 8% of the distal part of the cervix. The exact mechanism leading to physiological cervical ripening is not known. The biochemical events that have been implicated in cervical ripening are (1) a decrease in total collagen content, (2) an increase in collagen solubility, and (3) an increase in collagenolytic activity (Tang 2007)[22]. During cervical ripening, there is an influx of inflammatory cells intro the cervical stroma, which increases matrix metalloproteases and thereby leads to the degradation of collagen and cervical softening (Aronsson 2005)[23]. It has been proposed that these cells produce cytokines and prostaglandins that have an effect on extracellular matrix metabolism. It has also been shown that various prostaglandin analogies decrease the hydroxyl-proline content of pregnant cervix (Rath 1982)[24]. The action of misoprostol appeared to be mainly on the connective tissue stroma with evidence of disintegration and dissolution of collagen (El Rafaey 1994)[25].

Dose selection

Misoprostol dosage for the proposed extension of indication is the same, i.e. 400 µg as a single administration via oral route. This dose and route of administration is already approved for this proposed extension of indication in Europe (Gymiso in France) since 2004.

One prospective, comparative, randomised, double-blind study assessed the efficacy of 400 µg misoprostol via oral route in comparison with 200 µg, administered 10 to 16 hours before surgery, for cervix preparation in 551 women undergoing first trimester surgical abortion (Oppegaard 2004)[26]. In this study, cervical dilatation was significantly greater in the 400 µg group as compared with 200 µg (5.9 ±1.7 mm vs 5.4 ±1.5 mm, p=0.004).

Moreover, the 400 µg dose, and oral route for administration, are known to be commonly used, as described in the MYA study and in the last PSUSA overview of clinical pharmacology.

[22] Tang O.S., Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gyn Obs 2007; 99: S160-S167

[23] Aronsson A, Ulfgren AK, Ståbi B, Stavreus-Evers A, Gemzell-Danielsson K. The effect of orally and vaginally administered misoprostol on inflammatory mediators and cervical ripening during early pregnancy. Contraception. 2005 Jul;72(1):33-9

[24] Rath W, Theobald P, Kuhnle H, Kuhn W, Hilgers H, Weber L. Changes in collagen content of the first trimester cervix uteri after treatment with prostaglandin F2 alpha gel. Arch Gynecol 1982; 231: 107-110

[25] El-Refaey H, Calder L, Wheatley DN, Templeton A. Cervical priming with prostaglandin E1 analogues, misoprostol and gemeprost. Lancet 1994;343(8907):1207–9.

[26] Oppegaard KS, Abdelnoor M, Nesheim BI, Jerve F, Eskild A. The use of oral misoprostol for pre-abortion cervical priming: a randomised controlled trial of 400 versus 200 microg in first trimester pregnancies. BJOG. 2004 Feb;111(2):154-9

III.4 Clinical efficacy

III.4.1 Introduction

Efficacy data in this application consisted of published results of clinical studies comparing the efficacy of the administration of misoprostol 400 µg via oral route to the administration of placebo, no pre-treatment for cervix dilatation, or comparative active controls.

III.4.2 Efficacy studies

The efficacy of misoprostol 400 µg via oral route for cervical priming before first trimester surgical termination of pregnancy was assessed in three studies versus a placebo (Cakir 2005[27], Ngai 1999[28], Ngai 1995[29]), and two studies versus the standard of care, including no pre-treatment (Saxena 2008[30], Sharma 2005[31]).

The efficacy and safety of misoprostol 400 µg via oral route was also compared to the use of luminaria (MacIsaac 1999)[32], or the use of various other medications, including prostaglandin E2 derivatives (sulprostone (Schaub 1995)[33], dinoprostone (Sparrow 1998)[34]), prostaglandin E1 analogue (gemeprost) (Ngai 1995 geme)[35], and prostaglandin receptors antagonist (mifepristone) (Ngai 1996)[36].

In addition, supportive data from one non-comparative study and from the French observational study is provided.

Population

Women included in these studies were aged 19 to 31 years as a mean, with surgical abortion of early pregnancy, i.e. first trimester for most studies, or up to 14 weeks for MacIsaac study. The rate of nulliparous was above 50%, but very variable from one study to another one, and even within one study (Sharma 2005)[31] where statistical analyses had to be adjusted to take this factor into account.

Efficacy endpoints

Main efficacy endpoints were cervical dilatation, rate of women needing extra dilatation and duration of operation.

Primary endpoints

Cervical dilatation was the primary efficacy criterion in most studies. It was measured using the size of the largest Hegar's dilator that could be passed into the cervix without resistance in all studies but the MacIsaac study which used Pratt dilators to measure it.

[27] Cakir L, Dilbaz B, Caliskan E, Dede FS, Dilbaz S, Haberal A. Comparison of oral and vaginal misoprostol for cervical ripening before manual vacuum aspiration of first trimester pregnancy under local anesthesia: a randomized placebo-controlled study. Contraception. 2005 May;71(5):337-42.

[28] Ngai SW, Chan YM, Tang OS, Ho PC. The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. Hum Reprod. 1999 Aug;14(8):2139-42.

[29] Ngai SW, Tang OS, Lao T, Ho PC, Ma HK. Oral misoprostol versus placebo for cervical dilatation before vacuum aspiration in first trimester pregnancy. Hum Reprod. 1995 May;10(5):1220-2.

[30] Saxena P, Sarda N, Salhan S, Nandan D. A randomised comparison between sublingual, oral and vaginal route of misoprostol for pre-abortion cervical ripening in first-trimester pregnancy termination under local anaesthesia. Aust N Z J Obstet Gynaecol. 2008 Feb;48(1):101-6. doi: 10.1111/j.1479-828X.2007.00809.x.

[31] Sharma S, Refaey H, Stafford M, Purkayastha S, Parry M, Axby H. Oral versus vaginal misoprostol administered one hour before surgical termination of pregnancy: a randomised controlled trial. BJOG. 2005 Apr;112(4):456-60.

[32] MacIsaac L, Grossman D, Balistreri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstet Gynecol. 1999 May;93(5 Pt 1):766-70

[33] Schaub B, Fuhrer P, Sainte-Rose D. [Randomized study of sulprostone versus misoprostol in the cervical preparation before elective abortion in nulliparous women]. J Gynecol Obstet Biol Reprod (Paris). 1995;24(5):505-10

[34] Sparrow MJ, Tait JD, Stone PR. Vaginal dinoprostone versus oral misoprostol for predilatation of the cervix in first trimester surgical abortion. Aust N Z J Obstet Gynaecol. 1998 Feb;38(1):64-8

[35] Ngai SW, Yeung KC, Lao T, Ho PC. Oral misoprostol versus vaginal gemeprost for cervical dilatation prior to vacuum aspiration in women in the sixth to twelfth week of gestation. Contraception. 1995 Jun;51(6):347-50

[36] Ngai SW, Yeung KC, Lao T, Ho PC. Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study. Br J Obstet Gynaecol. 1996 Nov;103(11):1120-3

A preoperative cervical dilatation of 7 mm has, in previously randomised controlled trials, been classified as a 'satisfactory' achievement (de Jonge 2000)[37].

Efficacy results

Misoprostol dosage

The selected dose is considered adequately substantiated. In order to fond the lowest efficient dosage for misoprostol, data from two studies which directly compared the use of misoprostol 200 µg and 400 µg for cervical preparation, were analysed.

In a clinical prospective, randomised, double-blind study dedicated to compare the efficacy of a single 400 µg dose of oral misoprostol vs a single 200 µg dose oral misoprostol 10-16 hours before surgery for cervical priming before surgical termination of early (7-12 weeks of amenorrhea) pregnancy, cervical dilatation was significantly greater with 400 µg (5.9 ±1.7 vs 5.4 ±1.5 mm, p<0.001) (Oppegaard 2004)[26].

In a placebo-controlled study, cervical dilatation was significantly greater following administration of 400 µg misoprostol 3 hours before surgery as compared with misoprostol 200 µg (7.2 ±1.0 vs 6.6 ±0.9 mm, p<0.05). The difference between each misoprostol group and the placebo group (5.5 ±1.4) was also significant (p<0.01) (Ngai 1999)[28].

As the threshold of 7 mm was considered as a 'satisfactory' achievement (de Jonge 2000)[37], the dosage of 400 µg was considered the most appropriated from an efficacy point of view.

Time between misoprostol administration and surgery

Although a 12 hour pretreatment may have been considered preferable for a maximum dilatation of the cervical canal, a 3 hour period in generally considered sufficient, and easier to comply with from a practical point of view (Bygdeman 1984)[38].

In the studies presented in this dossier, one study assessed the efficacy of misoprostol 400 µg administered orally 3 or 12 hours before surgery in comparison with sulprostone infusion (Schaub 1995)[33]. Cervical dilatation was significantly higher when misoprostol was administered 12 hours before surgery as compared with 3 hours (8.2 ±1.3 vs 7.2 ±2.2, p=0.04), but there was an increased risk for partial expulsion (6% vs 0%, NS).

Therefore, the optimal schedule was considered to be the administration of misoprostol 3 hours before the operation.

Misoprostol route of administration

As the currently approved route of administration for MisoOne is the oral route, and as no additional development was performed for other routes of administration, the efficacy data provided are only based on the oral route.

Efficacy results with misoprostol 400 µg via oral route administered 3 hours before surgery

Cervical dilatation was the primary criterion for efficacy assessment in most studies. All placebo-controlled studies demonstrated the superiority of misoprostol 400 µg via oral route for cervical dilatation. When administered 3 hours before surgery in placebo-controlled studies, cervical dilatation after misoprostol 400 µg via oral route was 6.6 to 7.2 mm, while following placebo it was 3.4 to 5.5 (Table 2.5.4-1).

Misoprostol 400 µg oral route was also associated with a significantly greater cervical dilatation in the study versus no pre-treatment for cervical preparation where misoprostol was administered 3 hours before surgery (Table 2.5.4-1).

[37] de Jonge ET, Jewkes R, Levin J, Rees H. Randomised controlled trial of the efficacy of misoprostol used as a cervical ripening agent prior to termination of pregnancy in the first trimester. S Afr Med J 2000; 90(3):256–262

[38] Bygdeman M. The use of prostaglandins and their analogues for abortion. Clinics in Obstetrics and Gynaecology 1984; 11: 573-584

Table 2.5.4-1 : Cervical dilatation in comparative studies vs placebo or no pre-treatment

Study	Misoprostol 400µg oral		Control group		Cervical dilatation		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
Vs placebo							
Cakir 2005	40	3h	Placebo 40	3h	6.6mm ±1.5	3.4mm ±2	<0.001
Ngai 1999	40	3h	Placebo 44	3h	7.2mm ±1.0	5.5mm ±1.4	<0.05
Ngai 1995	*36*	*12h*	*Placebo 39*	*12h*	*Nulliparous 7.4mm ±2.0 Multiparous 9.2mm ±1.7*	*Nulliparous 4.1mm ±1.4 Multiparous 6.5mm ±1.5*	*<0.001*
Vs no pre-treatment							
Saxena 2008	50	3h	No pre-treatment 50	-	8.2mm ±2.6	1.9mm ±1.2	<0.001
Sharma 2005	*39*	*1h*	*No pre-treatment 30*	-	*7.4mm ±1.3*	*6.3mm ±1.6*	*0.01 0.06 (adjusted)*

Regarding the rate of women for whom additional dilatation was needed in the clinical studies described above: In the only placebo-controlled study where this result was provided, there was a significant difference with 90% needing additional dilatation in the placebo group versus 10% in the misoprostol group when the medication was administered 3 hours before surgery (Table 2.5.4-2).

Table 2.5.4-2 : Need for extra dilatation in comparative studies vs placebo or no pre-treatment

Study	Misoprostol 400µg oral		Control group		Need for additional dilatation (% women)		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
Vs placebo							
Cakir 2005	40	3h	Placebo 40	3h	10%	90%	<0.001
Ngai 1999	40	3h	Placebo 44	3h	NA	NA	
Ngai 1995	*36*	*12h*	*Placebo 39*	*12h*	*NA*	*NA*	
Vs no pre-treatment							
Saxena 2008	50	3h	No pre-treatment 50	-	NA	NA	
Sharma 2005	*39*	*1h*	*No pre-treatment 30*	-	*NA*	*NA*	

The duration of surgery was significantly decreased, probably mainly due to data in primiparous in most studies vs placebo or no pre-treatment following administration of misoprostol 400 µg via oral route 3 hours before surgery; it was not decreased in one study, but the difference was not statistically significant (Table 2.5.4-3) (Ngai 1999)[28].

Table 2.5.4-3 : Duration of operation in comparative studies vs placebo or no pre-treatment

Study	Misoprostol 400µg oral		Control group		Duration of operation (min)		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
Vs placebo							
Cakir 2005	40	3h	Placebo 40	3h	3.9 ± 1	5.1 ± 1	<0.001
Ngai 1999	40	3h	Placebo 44	3h	5.8 ± 2.3	4.9 ± 2	NA
Ngai 1995	*36*	*12h*	*Placebo 39*	*12h*	*Nulliparous: 6.5 ± 5 Multiparous: 7.1 ± 3.5*	*Nulliparous: 14.5 ± 9 Multiparous: 6.9 ± 2.5*	*Nulliparous: <0.0001 Multiparous: NS*
Vs no pre-treatment							
Saxena 2008	50	3h	No pre-treatment 50	-	4.9 ± 1.7	6.2 ± 1.9	<0.01
Sharma 2005	*39*	*1h*	*No pre-treatment 30*	-	*NA*	*NA*	

When administered 3 hours before surgery in placebo-controlled and in studies vs no pre-treatment,

- cervical dilatation was significantly increased after misoprostol 400 µg via oral route. It was 6.6 to 8.2 mm, depending upon studies, while a threshold of 7 has been considered as a 'satisfactory' achievement (de Jonge 2000)[37].
- the rate of women for whom additional dilatation was needed was significantly decreased.
- duration of surgery was significantly decreased.

Comparative benefits

Misoprostol 400 µg oral route was compared to other effective treatments for cervix preparation before first trimester surgical abortion. It was compared to the use of laminaria (MacIsaac 1999)[32], or to the use of various other medications, including prostaglandin E2 derivatives (sulprostone, that has no marketing authorisation in this for the cervical preparation before surgical abortion during first trimester) (Schaub 1995)[33] dinoprostone (Sparrow 1998)[34], prostaglandin E1 analogue (gemeprost) (Ngai 1995 geme)[35], and prostaglandin receptors antagonist (mifepristone) (Ngai 1996)[36].

Only one study assessed the administration of misoprostol 400 µg 3 hours before surgery in comparison with active techniques or medications (Schaub 1995)[33]. Therefore all studies will be analysed below.

Regarding cervical dilatation, when compared to other techniques or medications, there was no significant difference vs laminaria, or mifepristone, while the efficacy of misoprostol 400 µg via oral route was significantly greater than that of gemeprost; 1 mg via vaginal route; cervical dilatation after sulprostone was significantly greater vs misoprostol 400 µg administered 3 hours before surgery (Table 2.5.4-4).

The range of cervical dilatation data was homogeneous in all studies but the MacIsaac study which used Pratt dilators to measure it. In the other studies, cervical dilatation was measured using the size of the largest Hegar's dilator that could be passed into the cervix without resistance.

Table 2.5.4-4 : Cervical dilatation in comparative studies vs other techniques or medications

Study	Misoprostol 400µg oral		Control group		Cervical dilatation		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
MacIsaac 1999	45	4h	Laminaria 14	4h	24.2mm ±4.8	25.9mm ±5.8	NS
Schaub 1995	30	3h	Sulprostone 500µg 30	12h	7.2mm ± 12.2	8.6mm ± 1.3	0,02 in favour of sulprostone
Sparrow 1998	*160*	*≥1h*	*Dinoprostone 3mg 153*	*12h*	*NA*	*NA*	*NA*
Ngai 1995 gemeprost	*32*	*12h*	*Gemeprost 1mg 32*	*12h*	*8.1mm ±1.7mm*	*7.0mm ±1.7mm*	*<0.02*
Ngai 1996	*45*	*12h*	*Mifepristone 200mg 48*	*36h*	*8.0mm ±1.6mm*	*7.7mm ±1.2mm*	*NS*

There was few information regarding the rate of women for whom additional dilatation was needed in the clinical studies described above. In the only active comparator-controlled study where this result was provided, there was no significant difference with a rate of 64% women regarding additional dilatation in the misoprostol group versus 50% in the laminaria group (Table 2.5.4-5).

Table 2.5.4-5 : Need for extra dilatation in comparative studies vs other techniques or medications

Study	Misoprostol 400µg oral		Control group		Need for additional dilatation (% women)		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
MacIsaac 1999	*45*	*4h*	*Laminaria 14*	*4h*	*64%*	*50%*	*NS*
Schaub 1995	30	3h	Sulprostone 500µg 30	12h	NA	NA	
Sparrow 1998	*160*	*≥1h*	*Dinoprostone 3mg 153*	*12h*	*NA*	*NA*	
Ngai 1995 gemeprost	*32*	*12h*	*Gemeprost1mg 32*	*12h*	*NA*	*NA*	
Ngai 1996	*45*	*12h*	*Mifepristone 200mg 48*	*36h*	*NA*	*NA*	

Regarding duration of surgery, in the studies vs active control where this information was available, there was no significant difference between misoprostol and comparators (Table 2.5.4-6).

Table 2.5.4-6 : Duration of operation in comparative studies vs other techniques or medications

Study	Misoprostol 400µg oral		Control group		Duration of operation (min)		p
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	
MacIsaac 1999	*45*	*4h*	*Laminaria 14*	*4h*	*NA*	*NA*	
Schaub 1995	30	3h	Sulprostone 500µg 30	12h	NA	NA	
Sparrow 1998	*160*	*≥1h*	*Dinoprostone 3mg 153*	*12h*	*NA*	*NA*	
Ngai 1995 gemeprost	*32*	*12h*	*Gemeprost 1mg 32*	*12h*	*5.5 ± 2.7*	*7.0 ± 3.4*	*NS*
Ngai 1996	*45*	*12h*	*Mifepristone 200mg 48*	*36h*	*5.0 ± 2.2*	*4.5 ± 1.6*	*NS*

In studies comparing misoprostol 400 µg oral route to other efficient techniques or medications for cervical ripening before surgical termination of first trimester pregnancy, the only significant differences regarded cervical dilatation significantly greater with misoprostol as compared with 1 mg vaginal gemeprost, and significantly lower with misoprostol as compared with sulprostone infusion (that has no marketing authorisation for the cervical preparation before surgical abortion during first trimester).

III.4.3 Supportive studies

Two other studies provide information regarding the use of misoprostol 400 µg per os for cervical preparation before surgical abortion during first trimester: One observational non comparative study (Edwards 1994)[39] and one observational study dedicated to assess cervical preparation procedures in France in real life practice (MYA study)[40].

The first study confirmed the efficacy of misoprostol 400 µg administered via oral route less than 1 hour before surgery with 93% of cervices considered as not difficult to dilate (Edwards 1994)[39].

The data from the French observational study dedicated to assess the pre-treatment used in real practice for cervical preparation before surgical abortion during first trimester showed that surgical abortion is almost systematic in the French practices, and that misoprostol only was the most commonly prescribed regimen for the cervix preparation, with 302/510 (59%) women who underwent surgery who received misoprostol alone. Misoprostol was most often administered as a single 400 µg course per os, 3 hours before surgery. Mean corresponding cervical dilatation was 9.1 mm (MYA study)[40].

III.4.4 Conclusion clinical efficacy

The published literature presented to support efficacy of misoprostol in a oral dose of 400 µg in the requested indication is sufficiently documented.

III.5 Clinical safety

III.5.1 Introduction

As misoprostol administration for this new indication is similar to the one of the current indication, i.e. same dosage, same route of administration, single administration, no change in the known safety profile is anticipated.

However, possible interactions of misoprostol administration with surgery, i.e. intra-operative blood loss and interaction with anesthetics were analyzed.

[39] Edwards D, Aitken RE, Begg AF, MacKay PM, Marchant RM. Predilatation of the cervix before suction curettage for therapeutic abortion in early pregnancy. Aust N Z J Obstet Gynaecol. 1994 Feb;34(1):103-4

[40] MYA Study. Observational study on the cervical preparation prior to surgical abortion in real life conditions. Study Report. 20.06.2018.

III.5.2 Overall safety profile

AEs following a single administration of misoprostol 400 µg are summarised in the current SmPC. The side effects of misoprostol are usually an extension of the pharmacological action and of the drug bioavailability. The most common adverse reactions are gastrointestinal disorders e.g. nausea, vomiting, diarrhoea and abdominal pain.

Adverse reactions reported in the SmPC are similar for MisoOne (currently indicated only for first trimester medical abortion) and for Gymiso (indicated for first trimester medical abortion and for cervical preparation before surgical abortion during first trimester), with one difference regarding the presence of very rare cases of uterus rupture associated with the use of misoprostol for cervical preparation before surgical abortion during first trimester.

III.5.3 Safety data in literature clinical studies

Comparative studies vs placebo or no-treatment

Reported AEs were mainly pain (reported by 20-70% of women treated with misoprostol 400 µg oral route 3 hours before surgery vs 0-15% in the placebo group), gastro-intestinal disorders with nausea in 5-57% of misoprostol women vs 2-17.5% in placebo or no-treatment groups, vomiting in 2-10% of misoprostol women vs 0-5% in placebo or no-treatment groups, and diarrhoea in 5% misoprostol women vs 0-2.5% in placebo or no-treatment groups. Vaginal bleeding was more frequent in women treated with misoprostol (12.5-52.5%) as compared with placebo (0-2.5%), as expected (Table 2.5.5-1).

AEs following single administration of 400 µg misoprostol via oral route reported during clinical studies vs placebo or no-treatment were consistent with the known misoprostol safety profile.

Table 2.5.5-1 : Adverse Events before surgery in comparative studies vs placebo or no-treatment

Study	Miso 400µg oral		Control group		Pain		Nausea		Vomiting		Diarrhoea		Headache		Fever		Vaginal bleeding/spotting	
	n	Time before surgery	Control/n	Time before surgery	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control
Vs placebo																		
Cakir 2005	40	3h	Placebo/40	3h	70%	15%	57.5 %	17.5%	10%	5%	5%	2.5%	0	7.5%	5%	0	52.5%	2.5%
Ngai 1999	40	3h	Placebo/44	3h	20%	0	5%	4.5%	0	0	0	0	NA	NA	NA	NA	12.5%	0
Ngai 1995	36	12h	Placebo/39	12h	6%	3%	6%	3%	0	0	0	0	NA	NA	NA	NA	14%	3%
Vs no pre-treatment																		
Saxena 2008	50	3h	No pre-treatment/50	-	38%	NA	10%	2%	2%	0	0	0	NA	NA	6%	0	NA	NA
Sharma 2005	39	1h	No pre-treatment/30	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

In comparative studies vs other techniques or medications

There were large differences in rates of women reporting pain in the comparative studies with higher rates in the misoprostol group vs laminaria (76% vs 50%), vs dinoprostone (78% vs 19%) and vs mifepristone (47% vs 23%). Pain rate was lower with misoprostol vs sulprostone (53% vs 80%) and vs gemeprost (3% vs 12%). Regarding gastro-intestinal AEs, the main difference regarded the occurrence of nausea higher following sulprostone as compared with misoprostol (43% vs 15%). Regarding bleeding before surgery, the rates were higher vs misoprostol with sulprostone (36% vs 12%) and with gemeprost (22% vs 6%), while it was lower with mifepristone (25% vs 49%) (Table 2.5.5-2).

The rate of partial expulsions was significantly higher following sulprostone as compared with misoprostol.

A better tolerability was demonstrated for misoprostol vs sulprostone and vs gemeprost.

Table 2.5.5-2 : Adverse Events before surgery in comparative studies vs other technique or medications

Study	Miso 400µg oral		Control group		Pain		Nausea		Vomiting		Diarrhoea		Fever		Vaginal bleeding/spotting		Haemorrhage	
	n	Time before surgery	Control/n	Time before surgery	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control	Miso	Control
MacIsaac 1999	45	4h	Laminaria/ 14	4h	76%	50%	NA	NA	NA	NA	NA	NA	NA	NA	5%	NA	4%	0
Schaub 1995	30	3h	Sulprostone 500µg/30	12h	53%	80%	15%	43%	-	-	15%	7%	2%	7%	12%	36%	NA	NA
Sparrow 1998	160	≥1h	Dinoprostone 3mg/153	12h	78%	19%	10%	3%	NA	NA	NA	NA	NA	NA	12%	5%	NA	NA
Ngai 1995 gemeprost	32	12h	Gemeprost 1mg/32	12h	3%	12%	6%	16%	3%	3%	NA	NA	NA	NA	6%	22%	NA	NA
Ngai 1996	45	12h	Mifepristone 200mg/48	36h	47%	23%	18%	25%	22%	21%	0	2%	NA	NA	49%	25%	NA	NA

In studies assessing different dosages

In the Oppegaard study that compared oral administration of 200 µg and 400 µg misoprostol via oral route, the occurrence of pre-operative bleeding was significantly more frequent in women who received 400 µg (37% vs 15%, p<0.001); as the occurrence of pain (8% vs 3%, p=0.002).[26]

In the Ngai study (1999)[28], there was no difference regarding AEs between 400 µg oral route and 200 µg oral route.

However, the large comparative study of Oppegaard showed that the occurrence of pre-operative bleeding was significantly more frequent in women who received 400 µg (37% vs 15%, p<0.001); as the occurrence of pain (8% vs 3%, p=0.002).[26]

Pre-operative bleeding and pain are therefore added to the AE list in section 4.8 of the SmPC and section 4 of the PL.

In supportive studies

Data from the non-comparative Edwards study were consistent with the known misoprostol safety profile with 84% women complaining of mild or moderate abdominal cramping pain 30-40 minutes after 400 mg of misoprostol, vaginal bleeding reported in 16% women and nausea/vomiting in 5%. No new safety findings for MisoOne were received from this study.[39]

AEs of special interest

Intra-operative blood loss

There was no increase in intra-operative blood loss in women who received misoprostol. The administration of misoprostol 400 µg via oral route was associated with a significant decrease in intra-operative blood loss as compared with placebo in most studies (Table 2.5.5-3).

Table 2.5.5-3 : Intra-operative blood loss in comparative studies

Study	Misoprostol 400µg oral		Control group		Intra-operative blood loss (mL)		
	n	Time before surgery	Control n	Time before surgery	Misoprostol	Control	p
Vs placebo							
Cakir 2005	40	3h	Placebo 40	3h	66 ± 16	73 ± 17	NS
Ngai 1999	40	3h	Placebo 44	3h	88 ± 71	128 ± 123	<0.05
Ngai 1995	*36*	*12h*	*Placebo 39*	*12h*	*Nulliparous: 33.6 ± 28 Multiparous: 40 ± 28*	*Nulliparous: 98.0 ± 53.0 Multiparous: 98.0 ± 53.0*	*Nulliparous: <0.01 Multiparous <0.02*
Vs no pre-treatment							
Saxena 2008	50	3h	No pre-treatment 50	-	17.7 ± 7.3	21.4 ± 8.1	<0.02
Sharma 2005	*39*	*1h*	*No pre-treatment 30*	-	*NA*	*NA*	

Interaction with drugs used during surgical abortion
Drugs during surgical abortion are mainly analgesics and anaesthetics. However, there is no interaction with these medications described in MisoOne SmPC.

III.5.4 Post marketing experience
The last periodic safety update report single assessment (PSUSA 2018)[41] procedure for medicinal products containing misoprostol indicated for termination of early pregnancy (medical termination of early pregnancy and for cervical preparation before surgical abortion during first trimester) covered the period from 1 June 2015 to 31 May 2017.
Based on the PRAC Rapporteur review of data on safety and efficacy, it is considered that the risk-benefit balance of medicinal products containing misoprostol for termination of early pregnancy remains unchanged in the approved indication of termination of early pregnancy.

III.6 Risk Management Plan

The RMP has been adequately updated (version 6.2). The summary of safety concerns is now as follows:

Important identified risks	• Congenital anomaly • Misuse • Uterine haemorrhage • Cardiovascular disorder
Important potential risks	--
Missing information	• Renal impairment • Hepatic impairment

III.6.1 Additional risk minimization measures (aRMM)
The risk minimization measures which were already in place are not necessary for the new indication, because the product is given under controlled circumstances. As a result, the educational material kit agreed in the DCP has not been updated.

[41] PSUSA. Active Substance: misoprostol. Procedure PSUSA/00010354/201705. Version 2, 5 Jan 2018

According to the current legislation (Directive 2001/83/EC), the previously agreed educational material kit is an Article 21a condition[42] to the marketing authorisation. As a new indication has been approved in NL/H/2355/001/II/11, it was considered to be a good time to regard the earlier conditions also as Article 21a condition. This does not change the content of this educational kit or the obligations which were previously agreed for this educational kit.

The final content, lay-out, target audience, and distribution method should be agreed with individual national competent authorities at national level.

III.7 Discussion on the clinical aspects

Benefits
The literature data regarding misoprostol 400 µg via oral route for cervical preparation before surgical abortion during first trimester provided the following results:

When administered 3 hours before surgery in placebo-controlled and in studies vs no pre-treatment,
- cervical dilatation was significantly increased after misoprostol 400 µg via oral route. It was 6.6 to 8.2 mm, depending upon studies, while a threshold of 7 has been considered as a 'satisfactory' achievement (de Jonge 2000)[37].
- the rate of women for whom additional dilatation was needed was significantly decreased.
- duration of surgery was significantly decreased.

In studies comparing misoprostol 400 µg oral route to other efficient techniques or medications, the only significant differences regarded cervical dilatation significantly greater with misoprostol as compared with 1 mg vaginal gemeprost, and significantly lower with misoprostol as compared with sulprostone infusion (no marketing authorisation for the cervical preparation before surgical abortion during first trimester).
The proposed dosage, route of administration and delay between misoprostol intake and surgery are confirmed by real practice data with 59% women receiving misoprostol alone, most often administered as a single 400 µg course, per os, 3 hours before surgery (MYA study)[40].

Risks
The safety of a single administration of 400 µg misoprostol via oral route is well known. Based on safety data in the literature, no change is expected associated with the extension of indication to cervical preparation before surgical abortion during first trimester.

Overall
The published literature presented sufficiently support an adequate efficacy and acceptable safety profile of misoprostol in a oral dose of 400 µg in the requested indication.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

IV.1 Extension of the indication
After having considered the available evidence, it is concluded that the benefit-risk balance of the extension of the MisoOne indication with: *"Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester"* is positive. The clinical benefit and safety is sufficiently demonstrated to extend the indication.

[42] *Article 21a condition of Directive 2001/83/EC*
Additional risk minimization measures (including educational material)
Additional risk minimization activities are in place for this medicinal product. Educational material kit to communicate on appropriate usage of MisoOne in medical termination of pregnancy for healthcare professionals and patients for the safety concerns misuse, teratogenicity, toxic and septic shock, uterine haemorrhage, abdominopelvic pain, and cardiovascular disorders. The kit consists of educational material for healthcare professionals, and a brochure and safety card for patients.

Proposed dose recommendation
Misoprostol is taken as a single 400 microgram oral dose 3 to 4 hours before surgical operation.
Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

The variation procedure (NL/H/2355/001/II/011) was finalised on 19 June 2019.

As the available analysis provides information relevant for the prescriber the RMS and CMS agree that inclusion of information concerning the studies in the SmPC of MisoOne is appropriate.

IV.2 Addition of wording in the product information
The SmPC is adequately updated (see section V).

V CHANGES IN PRODUCT INFORMATION

The changes to the SmPC for section 4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 5.1 in the context of this variation are presented below. Added text is underlined, strike-through text was deleted.

4.1 Therapeutic indications

Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea (see section 4.2).

Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester.

Misoprostol is indicated in adults.

4.2 Posology and method of administration

Posology

- Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea:

Misoprostol is taken as a single 400 microgram oral dose 36 to 48 hours after taking a single 600 mg oral dose of mifepristone. Information on the posology of mifepristone can be found in the product information of mifepristone.

Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

- Cervix uteri preparation prior to surgical termination of pregnancy during the first trimester: Misoprostol is taken as a single 400 microgram oral dose 3 to 4 hours before surgical operation.
  Vomiting within 30 minutes after the intake could lead to a decrease in misoprostol efficacy: oral intake of a new misoprostol 400 microgram tablet is recommended in this case.

Paediatric population
Only limited data is available on the use of misoprostol in adolescents.

Method of administration
Misoprostol tablets are **for oral use only** and should not be administered by any other route of administration.

4.3. Contraindications

- *In all instances*

- Hypersensitivity to misoprostol or other prostaglandins, or to any of the excipients listed in section 6.1
- Pregnancy not confirmed by ultrasound scan or biological tests
- Suspected ectopic pregnancy
- ~~Contraindication for mifepristone.~~

- *For medical termination of pregnancy indication, in combination with mifepristone*

- Contraindication for mifepristone.
- Pregnancy beyond 49 days of amenorrhea,

~~As~~ When misoprostol is used in combination with mifepristone, please refer to the contraindications for this mifepristone as well.

4.4. Special warnings and precautions for use

- ***In all instances***

In the absence of specific studies, the ~~combination of the sequential use of mifepristone and~~ misoprostol is not recommended for use in patients with:
- Malnutrition
- Hepatic failure
- Renal failure

Warnings
Because of its abortifacient properties, misoprostol should never be used in a woman with an ongoing pregnancy who wants to complete it.
The age of the pregnancy must be determined from the questioning and the clinical examination of the patient. Uterine ultrasound is always recommended.

~~***Misoprostol MUST BE USED by oral route only:***~~

~~***- at a dose not higher than 400 microgram***~~
~~***- after a previous administration of 600 mg mifepristone***~~
~~***- Within the 36 – 48 hour interval after mifepristone intake***~~

~~**Use of off label regimen enhances ALL risks related to the method**~~

~~This method requires an active involvement of the woman who should be informed of the method's requirements:~~
- ~~the necessity to combine treatment with mifepristone to be administered 36 – 48 hours before administration of this product,~~
- ~~the need for a follow-up visit within 14 to 21 days after the intake of mifepristone in order to check for complete expulsion,~~
- ~~the possible failure of the method, leading to a pregnancy termination by a second termination of pregnancy procedure.~~

~~Because of possible acute effects of misoprostol, women should be fully counselled regarding the likely signs and symptoms they may experience and have direct access to the treatment centre by telephone or local access.~~
~~In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of mifepristone/misoprostol.~~

~~*Risks related to the method:*~~
~~The efficacy of the medical termination of pregnancy method decreases:~~
- ~~When the labelled regimen is not strictly applied,~~

- With parity

Failures
The non-negligible risk of an on-going pregnancy occurs in 1% of the cases where the medical termination of pregnancy was within 49 days of amenorrhea and after oral administration. This risk makes the follow-up visit mandatory in order to check that the expulsion is completed.
In rare case of non-complete expulsion, a surgical revision may be necessary.

Bleeding
The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 12 days or more after mifepristone intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The bleeding can occur very quickly after misoprostol intake, and sometimes later:
- in 60%, expulsion occurs within 4 hours following misoprostol intake
- in 40%, expulsion occurs within 24 to 72 hours following misoprostol intake.

Rarely the expulsion may occur before misoprostol administration (around 3% of cases). This doesn't preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go in the event of any problems emerging, particularly in the case of excessive vaginal bleeding. This is bleeding that lasts longer than 12 days and/or that is heavier than the normal menstrual bleeding.

A follow-up visit must take place within a period of 14 to 21 days after the intake of mifepristone to verify by the appropriate means (clinical examination, together with beta-hCG measurement or ultrasound scan) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an undiagnosed ectopic pregnancy, and appropriate treatment should be considered.

Since heavy bleeding requiring haemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder or the level of anaemia.

In the event of an ongoing pregnancy diagnosed after the follow-up visit, termination by a second termination of pregnancy procedure will be proposed to the woman.

Infection
Serious cases (including fatal cases) oftoxic shock and septic shock following infections with atypical pathogens (*Clostridium sordellii* and *perfringens*, *Klebsiella pneumoniae*, *Escherichia coli*, group A *Streptococcus*), have been reported with the medical abortion, performed with unauthorised vaginal or buccal administration of misoprostol tablets.

Clinicians should be aware of this potentially fatal complication.

Other
Due to presence of castor oil, there is a risk of sensitization.

Teratogenicity
Patients who decide to continue the pregnancy after treatment must be informed of the risk of teratogenicity. This risk is inherent to the mifepristone and misoprostol or misoprostol alone regimen objective and is enhanced when regimens other than the one mentioned in section 4.2 Posology and method of administration is used. Exposure of the foetus to misoprostol or mifeprostone increases the risk of developing Moebius syndrome and/or an amniotic band syndrome and/or central nervous system

anomalies (see section 4.6). A second termination of pregnancy procedure shall be considered. In case of continuation of the pregnancy close monitoring by ultrasound scan must be performed in specialised centres.

Rhesus allo-immunisation
The termination of pregnancy requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

Precautions for use
Cardiovascular risk
Rare but serious cardiovascular accidents (myocardial infarction and/or spasm of the coronary arteries and severe hypotension) have been reported following the intra vaginal and intra muscular administration of a high dose of prostaglandin analogue, including misoprostol. For this reason, women with risk factors for cardiovascular disease (e.g. age over 35 years with chronic smoking, hyperlipidemia, diabetes) or established cardiovascular disease should be treated with caution.
~~*Rhesus allo-immunisation*~~
~~The medical termination of pregnancy requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.~~

Contraception initiation after ~~medical~~ termination of pregnancy
During clinical trials, new pregnancies occurred between embryo expulsion and the resumption of menses. Therefore, when a termination of pregnancy conducted ~~by medical procedure~~ is medically confirmed, it is recommended to start contraception immediately.

~~*Other*~~
~~The precautions related to mifepristone should also be followed.~~

- ***Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea***

Warnings

Misoprostol MUST BE USED by oral route only: - at a dose not higher than 400 micrograms
- after a previous administration of 600 mg mifepristone
- Within the 36 – 48 hours interval after mifepristone intake

Use of off label regimen enhances ALL risks related to the method

This method requires an active involvement of the woman who should be informed of the method's requirements:
- the necessity to combine treatment with mifepristone to be administered 36 – 48 hours before administration of this product,
- the need for a follow-up visit within 14 to 21 days after the intake of mifepristone in order to check for complete expulsion,
- the possible failure of the method, leading to a pregnancy termination by a second termination of pregnancy procedure.

Because of possible acute effects of misoprostol, women should be fully counselled regarding the likely signs and symptoms they may experience and have direct access to the treatment centre by telephone or local access.

~~**Warnings**~~

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of mifepristone/misoprostol.

Risks related to the method:

The efficacy of the medical termination of pregnancy method decreases:
- When the labelled regimen is not strictly applied,
- With parity

Failures
The non-negligible risk of an on-going pregnancy occurs in 1% of the cases where the medical termination of pregnancy was within 49 days of amenorrhea and after oral administration. This risk makes the follow-up visit mandatory in order to check that the expulsion is completed. In rare case of non-complete expulsion, a surgical revision may be necessary.

Bleeding
The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 12 days or more after mifepristone intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The bleeding can occur very quickly after misoprostol intake, and sometimes later:
- in 60%, expulsion occurs within 4 hours following misoprostol intake
- in 40%, expulsion occurs within 24 to 72 hours following misoprostol intake.

Rarely the expulsion may occur before misoprostol administration (around 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go in the event of any problems emerging, particularly in the case of excessive vaginal bleeding. This is bleeding that lasts longer than 12 days and/or that is heavier than the normal menstrual bleeding.

A follow-up visit must take place within a period of 14 to 21 days after the intake of mifepristone to verify by the appropriate means (clinical examination, together with beta-hCG measurement or ultrasound scan) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an undiagnosed ectopic pregnancy, and appropriate treatment should be considered.

Since heavy bleeding requiring haemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with haemostatic disorders with hypocoagulability, or with anaemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of haemostatic disorder or the level of anaemia.

In the event of an ongoing pregnancy diagnosed after the follow-up visit, termination by a second termination of pregnancy procedure will be proposed to the woman.

Infection
Serious cases (including fatal cases) of toxic shock and septic shock following infections with atypical pathogens (*Clostridium sordellii* and *perfringens*, *Klebsiella pneumoniae*, *Escherichia coli*, group A *Streptococcus*), have been reported with the medical abortion, performed with unauthorised vaginal or buccal administration of misoprostol tablets.
Clinicians should be aware of this potentially fatal complication.

Precautions for use
Other
The precautions related to mifepristone should also be followed.

- **Cervical preparation before first trimester surgical termination of pregnancy.**

Warnings

Misoprostol MUST BE USED by oral route only:
- at a dose not higher than 400 micrograms

Use of off label regimen enhances ALL risks related to the method

- No data are available on cervical preparation with misoprostol prior to surgical termination of pregnancy beyond the first trimester,

- The patient should be informed about the specificities about the surgical method: local or a general anaesthesia and short hospitalization required,

Failure rate
Success rate of surgical abortion is above 97.7%, which means that the failure rate is about 2.3%. This risk makes the follow-up visit mandatory in order to check that the abortion is completed. In rare case of abortion failed, another procedure may be necessary.

Bleeding
The patient should be informed of possible occurrence of heavy vaginal bleeding after taking misoprostol. Consequently, Misoprostol should be preferably taken at the treatment centre before the surgical procedure.

Risk of abortion before the surgical procedure
There is a risk of abortion before the surgical procedure, even though this risk is low.

Complication of the surgical procedure
Rare complications include uterus damage.

~~A follow-up visit must take place within a period of 14 to 21 days after the surgical termination of pregnancy. In case of fever, pain, bleeding that occur after the surgery this visit should be done immediately.~~

Due to potential uterine rupture (very rare in the first trimester) and due to the lack of safety and efficacy studies in a scarred uterus, misoprostol must be used with caution in case of uterine fragility, in particular in case of significant multiparity or scarred uterus.
Misoprostol treatment must be systematically followed by surgical termination of pregnancy.

~~*Infection*~~
~~A rare risk of infection exists with the surgical procedure. To prevent this risk an antibioprophylaxy is strongly recommended in compliance with the local medical guidelines.~~
~~Serious cases (including fatal cases) of toxic shock and septic shock following infections with atypical pathogens (*Clostridium sordellii* and *perfringens*, *Klebsiella pneumoniae*, *Escherichia coli*, group A *Streptococcus*), have been reported with the medical abortion, performed with unauthorised vaginal or buccal administration of misoprostol tablets.~~
~~Clinicians should be aware of this potentially fatal complication.~~

A follow-up visit must take place within a period of 14 to 21 days after the surgical termination of pregnancy. In case of fever, pain, bleeding that occur after the surgery this visit should be done immediately.

4.6. Fertility, pregnancy and lactation

Pregnancy
Failure of pregnancy termination (continuing pregnancy) has been associated with a 3-fold increased risk of birth defects/malformations for ongoing pregnancies exposed to mifepristone and misoprostol or misoprostol alone, compared to control group (about 2%). In particular, prenatal exposure to misoprostol has been associated with Moebius syndrome (congenital facial paralysis leading to hypomimia, troubles of sucking and deglutition and eye movements, with or without limb defects) and with amniotic band syndrome (limb deformities/ amputations, especially clubfoot, acheiria, olygodactyly, cleft palate inter alia), and central nervous system anomalies (cerebral and cranial anomalies such as anencephaly, hydrocephaly, cerebellar hypoplasia, neural tube defects).

Women considering medical termination of pregnancy should be precisely counselled on the risks to their foetus if an abortion failure occurs and a second termination of pregnancy procedure is not desirable.

Consequently:
- Women should be informed, that due to the risk of failure of the ~~medical~~ method of pregnancy termination and to the risk for the foetus, the follow-up visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the follow-up visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by a second termination of pregnancy procedure.
- Should the patient wish to continue with her pregnancy, a careful ultrasound scan monitoring of the pregnancy, with a special attention to the limbs and head, must be established in a specialised centre.

Breast feeding
Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Misoprostol may also be excreted in breast milk and consequently, women should avoid breastfeeding while taking mifepristone and misoprostol or misoprostol alone.

Fertility
Misoprostol does not affect fertility. It is possible that the woman becomes pregnant again as soon as the termination of pregnancy is completed. Therefore it is important to inform the patient to start contraception immediately after the termination of the pregnancy is confirmed.

4.8. Undesirable effects

Reproductive system and breast disorders
Very common:
- Very common uterine contractions or cramping (10 to 45%) in the hours following misoprostol intake.
- Uterine bleeding

Common:
- Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Other gynaecological drugs, oxytocics - prostaglandins

ATC code: G02AD06

- *In all instances*

At the recommended dosage, misoprostol (a synthetic analogue of prostaglandin E1) induces contractions of smooth muscle fibres of the myometrium and a relaxation of the cervix uteri. The uterotonic properties of misoprostol should facilitate the opening of the cervix uteri.
At the recommended dosage, misoprostol should not involve cardiac, hepatic or renal undesirable effects.

- *Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea*

Misoprostol (~~a synthetic analogue of prostaglandin E_1~~) 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 microgram orally up to 49 days of amenorrhea.

~~At the recommended dosage, misoprostol induces contractions of smooth muscle fibres of the myometrium and a relaxation of the cervix uteri.~~ The uterotonic properties of misoprostol should facilitate the opening of the cervix uteri and the expulsion of intra-uterine remains.

~~At the recommended dosage, misoprostol should not involve cardiac, hepatic or renal undesirable effects.~~