COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sunmedabon combipack of mifepristone 200 mg tablet and misoprostol 4 x 0.2 mg vaginal tablets (mifepristone/misoprostol)

NL/H/4796/001

Date: 28 November 2022

This module reflects the scientific discussion for the approval of Sunmedabon. The procedure was finalised on 22 March 2012 in Sweden (SE/H/752/01/DC). After a transfer on 15 February 2019, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sunmedabon combipack of mifepristone 200 mg tablet and misoprostol 4 x 0.2 mg vaginal tablets, from Sun Pharmaceutical Industries Europe B.V. (The Netherlands).

The active substances are mifepristone and misoprostol. Mifepristone is a synthetic steroid with an antiprogestational action and misoprostol is a synthetic analogue of prostaglandin E1. For approved indications, see the Summary of Product Characteristics.

Following a discussion in CMDh and assessment of the full study report for the Warriner (Nepal) study, it was concluded that Sunmedabon has an acceptably high efficacy rate and a side effect and bleeding pattern that is comparable with other studies using similar regimens and a very low rate of serious adverse events.

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

II. QUALITY ASPECTS

II.1 Introduction

Sunmedabon is presented in the form of a combination pack containing tablets with 200 mg of mifepristone and four vaginal tablets with 0.2 mg of misoprostol (4×0.2 mg). The excipients are hydrogenated castor oil, microcrystalline cellulose, hypromellose and sodium starch glycolate. The tablets are packed in blisters.

II.2 Drug Substance

Misoprostol has a monograph in the Ph. Eur. Mifepristone does not have a monograph in the Ph. Eur.

Misoprostol is a clear, colourless or yellowish, oily hygroscopic liquid, practically insoluble in water and soluble in ethanol (96%). The structure of misoprostol has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Mifepristone is a light yellow to yellow crystalline powder, freely soluble in methanol and practically insoluble in water. The structure of mifepristone has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on

polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance
The active substance specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability of drug substance
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Pharmaceutical development
The product development has taken into consideration the physico-chemical characteristics of the active substances, such as poor aqueous solubility, hygroscopic properties, polymorphism and stability.

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. Sunmedabon tablets/vaginal tablets is formulated using excipients described in the current Ph.Eur.

Quality control of drug product
The tests and limits in the specifications are considered appropriate to control the quality of the finished products in relation to their intended purpose.

Stability of drug product
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All raw materials used in the product are of vegetable origin or has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sunmedabon has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sunmedabon is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The primary/secondary pharmacodynamic profiles as well as the safety pharmacology profile of the two substances are well-known and have adequately been presented in the nonclinical overview for Sunmedabon. The MAH has presented sufficient nonclinical data on the main areas of toxicological investigations, i.e. conventional toxicity studies, genotoxicity and reproductive toxicity. The toxicity profiles of both compounds were presented. The profiles in relatively low mifepristone-exposed animals were mainly related to primary or secondary effects of hormonal imbalances (antiprogesterone, anti-glucocorticoid and antiandrogenic activities). Gastrointestinal toxicity was mainly reported with misoprostol in rat and dog. Both compounds were tested negative in the testing programme that covers principally the conventional test battery of genotoxicity testing. The reproductive toxicity profiles have been investigated for each compound, mifepristone showed expected abortifacient activity and foetal malformations in rabbit at sub-abortifacient doses. Orally administered misoprostol has showed decreased number of live foetuses (decreased implantation/increased resorption) in rat and fetotoxicity (increased resorption, increased of cleft palate and reduced ossification) in mouse. The proposed SmPC 4.6 text for Sunmedabon is cautious and similar with that of mifepristone. The text is considered adequate, for example recommending surgical termination of pregnancy upon treatment failure. The animal data is adequately reflected. The SmPC text 5.3 regarding mifepristone is also similar to that of Mifegyne and is considered adequate.

The impurity limit profiles of the compounds do not suggest any safety problems. The lack of a local vaginal tolerance study of the misoprostol formulation is acceptable due to the well-known excipients used. A newly performed Phase I Envirmonmental Risk Assessment (ERA) does not implicate any risks to the environment.

In conclusion, the MAH has adequately presented a non-clinical evaluation of Sunmedabon. Sunmedabon can therefore be approved from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The combination regimen of mifepristone and a prostaglandin analogue as a non-surgical alternative to surgical termination of early intrauterine pregnancy is well established and has been in clinical use since mifepristone was first approved in France in 1988, in UK 1991 and in Sweden 1992. In 1999, mifepristone (Mifegyne) was approved via a mutual recognition procedure in several EU member states with France acting as reference member state.

The registered dose of mifepristone in Europe is 600 mg followed 36-48 hours later by 0,4 mg oral misoprostol when the duration of pregnancy is <49 days since the onset of last menstrual period. When the pregnancy is more advanced (i.e. 50 – 63 days since last menstrual period), the registered prostaglandin is gemeprost 1 mg vaginally.

It should be noted, however, that there is an approved alternative posology with 200 mg of mifepristone for pregnancies up to 63 days of amenorrhea, provided the subsequent prostaglandin is vaginal gemeprost as reflected in the EU Summary of Products Characteristics of Mifegyne: "Alternatively, 200 mg of mifepristone can also be used in a single oral dose, followed 36 to 48 hours later by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam".

Misopristol is a synthetic prostaglandin E1 analogue, initially developed for oral administration and available in a 200 µg dose for the treatment and prophylaxis of ventricular ulcus. Misopristol 200 µg is approved for medical abortion only in a few countries, whereas the off-label use of misoprostol for medical abortion (and for other obstetrical and gynaecological indications) is reported to be wide-spread and extensive within Europe, the USA and worldwide, most often by the vaginal route of administration.

The development of a combined product delivering both components necessary for medical abortion (i.e. mifepristone and misoprostol) is endorsed as it constitutes a measure to reduce the current widespread off-label use of a non-authorized misoprostol product, which is used vaginally although the product is intended for oral use, resulting in unpredictable doses and lack of pharmacovigilance activities.

IV.2 Pharmacokinetics

The dossier contained one pivotal pharmacokinetic study (WHO-A65037). This was a single dose parallel group study of either the test product, Sunmedabon, containing mifepristone tablets and misprostol vaginal tablets or Mifegyne and Cytotec.

The absolute bioavailability of mifepristone is approximately 40 % and variable. The relative bioavailability of different routes of administrations of misoprostol has been investigated by different researchers. Depending on type of formulation, the relative bioavailability differs.

On a general basis, vaginal administration results in higher bioavailability compared with oral administration and sublingual administration results in high maximal concentrations.

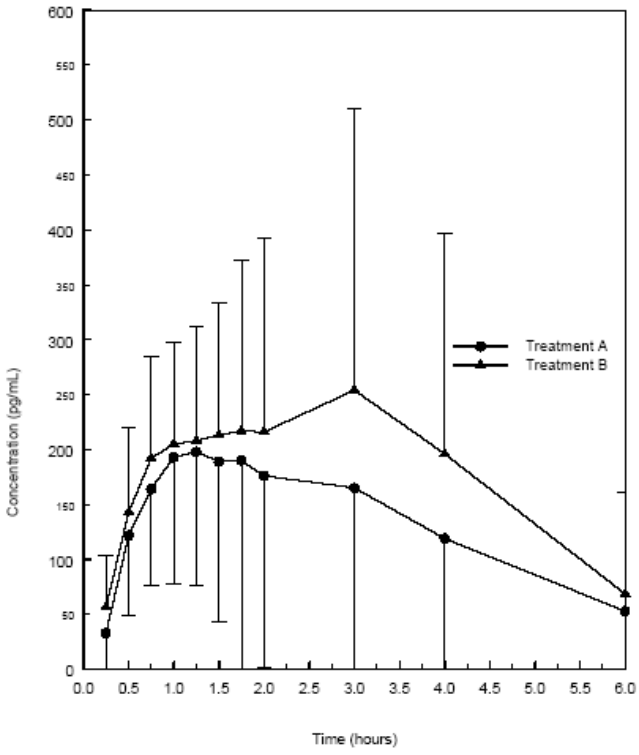
In study WHO-A65037, bioequivalence was demonstrated for mifepristone vs. Mifegyne for oral administration of the mifepristone tablet component in Sunmedabon. After vaginal administration of the misoprostol vaginal tablets in Sunmedabon and Cytotec 800 microgram, it was shown that the rate and extent of absorption of the misoprostol vaginal tablets was increased by approximately 70 % compared to Cytotec, see results and figure below.

Table 1. Mean (SD) pharmacokinetic parameters for misoprostol (n=30 and 31, test and reference).

Preparation	C_{max} (pg/ml)	t_{max}* (h)	$AUC_{0\text{-}t\ (0\text{-}6\ hours)}$ (pg·h/ml)
Test	420 (257)	2.63 (0.52-4.12)	1130 (620)
Reference	260 (217)	1.46 (0.58-6.02)	727 (598)
Ratio test/ref 90% CI	1.73 (1.27-2.35)	1.24 (1.00-1.80)	1.72 (1.25-2.37)

* t_{max} which is given as median (range), ratio is based on medians

Figure 1. Misoprostol concentrations after treatment A (Cytotec, 4 tablets) and treatment B (Sunmedabon, 4 vaginal tablets)

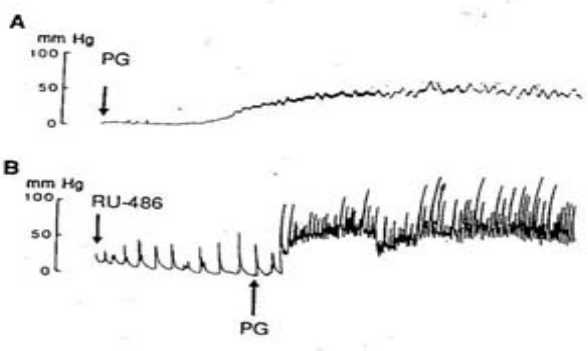


Since the pivotal WHO efficacy and safety study was performed with Cytotec, there is no knowledge about the potential undesirable effect difference with respect to the effects of misoprostol in Sunmedabon. References were provided in which the impact of sublingual administration with short effect duration and potentially higher degree of undesirable effects as a consequence of increased maximal concentrations were discussed. In an article by Aronsson et al. (2007), it is claimed that it is the time over a certain concentration that is important for the effect, not the exposure itself . Given the signs of highly increased rate and extent of absorption, the applicant was asked to discuss the appropriateness of the current misoprostol formulation in terms of safety.

IV.3 Pharmacodynamics

Medical abortion is based on the combined effects of an antiprogesterone and a prostaglandin on uterine contractility as described by Bygdeman and Swahn (1981) and illustrated in figure 2. Those effects have since then been established in numerous studies together with studies showing effects on the uterine cervix.

Figure 2. The effects on uterine contractility in early human pregnancy of an injectable prostaglandin (sulprostone) without (A) and with (B) pretreatment with an antiprogesterone (RU486=mifepristone).



IV.4 Clinical efficacy

Data from the pivotal placebo-controlled double-blind study sponsored by the WHO indicate that the combined effect of 200 mg mifepristone orally followed 36 to 48 hours later by 0,8 mg misoprostol (Cytotec) vaginally will provide medical abortion in pregnancies up to 63 days of amenorrhea with an efficacy that appears comparable to that of the already approved regimen 200 mg mifepristone orally followed by 1 mg gemeprost vaginally (table 2).

Table 2. Treatment outcome by amenorrhea duration after 200 mg mifepristone followed 36-48 hours later by various regimens of misoprostol from the pivotal WHO study (applied regimen shadowed).

Misoprostol treatment regimen	Days of amenorrhea	Complete abortion		Continuing pregnancy	
		N	%	N	%
O/O *Oral miso 0,8mg* *+ Oral miso 0,4x2xVII*	≤49 50-56 ≥57≤63	221 224 234	93,6 93,3 88,6	0 3 6	0,0 1,3 2,3
V/O *Vaginal miso 0,8mg* *+ Oral miso 0,4x2xVII*	≤49 50-56 ≥57≤63	228 229 244	94,6 93,1 96,1	0 1 0	0,0 0,4 0,0
V-only *Vaginal miso 0,8mg*	≤49 50-56 ≥57≤63	214 227 249	95,5 93,0 92,2	2 0 0	0,9 0,0 0,0
All	≤49 50-56 ≥57≤63 total	663 680 727 2070	94,6 93,2 92,3 93,3	2 4 6 12	0,3 0,5 0,8 0,5

Table 3. Efficacy of mifepristone 600 mg + oral or vaginal prostaglandins up to 49 days or up to 63 days of amenorrhea in pivotal studies originally used for registration of mifepristone in EU.

Study	Posology	N	Days of amenorrhea	Complete abortion %	Continuing pregnancy %
Peyron et al. 1993	Mife 600 + miso 0,4 orally	488	<49	96,9	0,8
Aubeny et al. 1995	Mife 600 + miso 0,4 ±0,2 orally	465 559	<49 50-63	95,3 92,1	1,3 3,2
Spitz et al. 1998	Mife 600 + miso 0,4 orally	827 1188	<49 50-63	92,0 80,6	1,0 6,0
FF/87/486/14	Mife 600 + geme 1 mg vag	157	<49	98,7	0
Urquhart et al. 1997	Mife 600 + geme 1 mg vag	337 620	<49 50-63	96,3 94,2	0,3

The efficacy of the applied regimen is also comparable to that of mifepristone 600 mg in combination with 0,4 mg misoprostol orally, as is the approved regimen for abortion up to 49 days of amenorrhea. For comparison, results are presented from the 5 pivotal phase III studies which were the basis for the European approval of 600 mg mifepristone followed 36-48 hours later by 400 µg misoprostol orally or gemeprost 1 mg vaginally, for termination of pregnancies up to 49 days of amenorrhea. Some of those studies also included women up to 63 days of amenorrhea (table 3).

The pivotal WHO study suggests that with an initial oral dose of 0.8 mg misoprostol, despite additional repeat oral doses, the efficacy remained lower than when misoprostol was initially given vaginally although the difference in complete abortion rate between oral and vaginal misoprostol up to 56 days of amenorrhoea was not statistically significant. In more advanced pregnancies, i.e. in women with length of amenorrhea >57 days, the vaginal route of 0.8 mg misoprostol (V/O and V-only groups) after 200 mg of mifepristone was significantly more effective than the oral route (O/O group) in achieving complete abortion. Women with >57 days of amenorrhea receiving misoprostol orally (O/O) had almost three times higher risk of failure (RR 2,9; 95% CI 1,4 to 5,8) than women receiving misoprostol vaginally with additional oral treatment (V/O). The RR of having a failure in women with >57 days of amenorrhea receiving misoprostol orally (O/O) was 1,5 times higher (RR 1,5; 95%CI 0,9 to 2,5) than in women receiving 0,8 mg misoprostol vaginally (V-only). Thus, the most effective of the three regimens tested in the pivotal WHO study was the one that gave 0,8 mg vaginal misoprostol followed by 0,8 mg oral misoprostol daily for 7 days (V/O).

Although the difference between the O/O and the V-only groups in complete abortion rate was not statistically significant, the O/O administration was associated with a 4,5 times higher risk of continuing live pregnancies when compared with the V-only group (RR 4,5; 95% CI 1,0 to 20,7).

The risk of continuing pregnancy increased with gestational age: out of the total of 9 continuing pregnancies in the O/O group, 6 were among women with length of amenorrhoea 57 days or more. Among women with length of amenorrhoea >57 days, continued administration of oral misoprostol (V/O group) further improved the efficacy compared with a single dose of 0.8 mg of vaginal misoprostol (V-only group). It should be emphasised that continuing pregnancy is a worse outcome after medical abortion than incomplete abortion as it may go unnoticed for a long time.

All the submitted studies have employed a single oral dose of 200 mg of mifepristone, although 600 mg of mifepristone has been the approved dose with demonstrated efficacy on both the outcomes of complete abortion and continuing pregnancy. As the submitted studies did not use different dosing of mifepristone, no further evaluation with regard to the mifepristone dose can be done from them.

Table 4. Efficacy of 600 mg vs 200 mg mifepristone in combination with 1 mg gemeprost vaginally for termination of pregnancy <57 days and 57-63 days of amenorrhea, respectively.

Study	Posology	N	Days of amenorrhea	Complete ab %	Continuing pregnancy %
WHO (1993)	Mife 600 + geme 1mg Mife 200 + geme 1mg	389 388	<57	94,3 93,8	0,3 0,5
WHO (2001)	Mife 600 + geme 1mg Mife 200 + geme 1mg	447 449	57-63	91,7 92,4	1,6 1,3

There are many published studies on the 200 mg dose of mifepristone in various combinations with different doses, routes of administration, and brands of prostaglandins. Based on previous randomized comparative studies by the WHO, the 200 mg dose of mifepristone seems established in combination with a potent prostaglandin with regard to the outcome complete abortion (table 4) (WHO Task Force, 1993, 2001).

In conclusion, data submitted indicate that the combined effect of 200 mg mifepristone orally followed 36-48 hours later by 0,8 mg misoprostol (as Cytotec) vaginally (applied regimen) will provide an effective method for medical abortion up to 63 days of amenorrhea. With the addition of a daily oral dose of 0,8 mg misoprostol to the initial vaginal dose, the efficacy was even better in pregnancies with a duration of amenorrhea >57 days. However, the simplicity of just one dose of vaginal misoprostol – in contrast to additional treatment for 7 days, as in the most effective regimen studied (V/O) – justifies the choice of regimen applied for with regard to expected compliance.

IV.5 Clinical safety

The adverse effects reported can be divided into those related to the early pregnancy situation (nausea, vomiting, breast tenderness, fatigue, dizziness, headache, fainting), to those related to the drugs (diarrhoea, fever defined as temperature >38ºC, and rash) and those related to the abortion process (lower abdominal pain, bleeding). The majority of adverse events, in particular gastrointestinal AEs, associated with medical abortion are related to the prostaglandin.

Whereas most adverse events were similar in the three groups in the pivotal WHO study, there were some differences between the three dose regimens in favour of the V-only regimen. The occurrence of nausea and vomiting was higher in the oral group than in the vaginal groups. Vomiting is a well-known misoprostol related side effects. Also, diarrhoea was significantly more often reported by women in the O/O or V/O groups. At 1, 2 and 3 hours after administration of misoprostol, diarrhoea was more frequent in the oral group than in the vaginal groups. At the two-week follow up visit, 26% of women who continued with oral misoprostol twice daily for one week (O/O and V/O groups) reported having suffered from diarrhoea, compared with only 9% of women in the V-only group who took placebo for a week.

There was no difference between treatment regimens with regard to estimated duration or amount of vaginal bleeding. There were in all 10 women who required surgical intervention for continuing vaginal bleeding or emergency incomplete abortion. There were 40 women with bleeding more or much more than in normal menses requiring uterotonics to stop bleeding. Blood transfusion was needed in 0.1% of all cases.

Suspected gynaecological infection was reported in 0.6% (13/2219) of patients. Most were presumptive infections based on clinical symptoms of fever, lower abdominal pain and vaginal bleeding. Endometritis was defined in 7 cases. There were no serious or fatal infections in the study and all of the infection cases were manageable by antibiotic therapy

and resulted in complete recovery. The incidence of fever (temperature >38°C) after administration of misoprostol, was higher in the oral group than in the vaginal groups at 1 hour but the opposite was found at 3 hours. After administration of misoprostol, the frequency of fever in the vaginal groups after 3 hours was 6% vs. 4.5% in the O/O group at 2 hours (P<0.001).

The issue whether vaginal misoprostol is causally associated with an increased risk of very severe rare infections caused by Clostridium sordellii cannot be resolved within this or other studies of limited size. So far, no causal relationship between those very severe cases and the use of mifepristone and vaginal misoprostol has been established. There have been no further reports on fatal cases. However, the extensive off label use of misoprostol has precluded common pharmacovigilance activities.

In a recent publication, the rates of serious infections dropped significantly from 0,93 to 0,06 per 1000 abortions in the US following a joint change in regimen from vaginal to buccal administration of misoprostol and routine STI testing/provision of antibiotics (Fjerstad et al., 2009). The change in clinical routines occurred as a result of the reports of 4 fatal cases. The study cannot determine to what extent the change from vaginal to buccal administration contributed to the reduction in relation to routine STI testing/provision of antibiotics or to the increased awareness of the risk of severe infection which followed the report of the fatal cases.

In conclusion, there was little difference in adverse events, lower abdominal pain and bleeding pattern between groups, whereas there were more gastro-intestinal adverse events in the groups taking oral misoprostol for 7 days. Thus, the regimen that was associated with the lowest frequency of adverse events was the mifepristone 200 mg followed 36-48 hours later by 0,8 mg misoprostol vaginally. The proposed regimen with 200 mg mifepristone followed 36-48 hours later by 0,8 mg misoprostol vaginally appears to be a safe medical method of abortion in otherwise healthy women with pregnancy duration of up to 63 days of amenorrhea.

As described above (pharmacokinetics), it was shown that the rate and extent of absorption of the misoprostol vaginal tablets was increased by approximately 70% for Sunmedabon compared to Cytotec after vaginal administration in study WHO-A65037. Regarding the issue of increased exposure to misoprostol in comparison with Cytotec that was used in the pivotal efficacy and safety study, this could be considered acceptable for the following reasons:

- Medical abortion with mifepristone and misopristol – as in Sunmedabon – is a single dose and single occasion administration.
- From many published clinical studies, there is no evidence to suggest that the higher exposure of misoprostol with the current product would reduce the abortifacient efficacy.
- Although common prostaglandin related gastrointestinal adverse events may occur slightly more often with higher exposure to misoprostol, there is little evidence from the pivotal study and from other published clinical studies that a higher exposure of

misoprostol will result in a clinically relevant increase in the frequency and severity of adverse events.
- A combination pack providing the complete set of drugs needed to perform a medical abortion will also allow regular pharmacovigilance activities including risk minimization and a Risk Management Plan (RMP).

The RMS therefore considered that the applicant had provided reasonable arguments for accepting the 70% higher bioavailability for misoprostol with the Sunmedabon formulation as compared to Cytotec. No efficacy concerns were foreseen and the higher exposure was considered unlikely to pose any major safety concerns, since misoprostol has been used in higher doses and via other administration routes with higher bioavailability (e.g. sublingual) and safety data from such use was presented. The need for an adequate RMP to reduce the risks associated with treatment failure, profuse bleeding and genital infection or a subsequent unwanted pregnancy was, however, emphasized. It was proposed that these activities should include a doctor's checklist, as well as a patient card to address both immediate risks and the long-term need to prevent a new unwanted pregnancy.

Agreement could not be reached during the DC procedure and concerns were maintained that the pharmacokinetic bridging study showed a much higher exposure of misoprostol with Sunmedabon compared to the reference product Cytotec used in all clinical studies referred to. In response to these concerns, a new published study (Warriner et al., 2011) was submitted, in which Sunmedabon (same product as in the current application) was given to >1000 pregnant women with gestational duration of <63 days. The primary aim of the study was to investigate whether efficacy/safety with Sunmedabon differed when administered by a mid-level health care provider or a doctor in rural Nepal. The primary outcome parameter was complete abortion without surgical intervention within 30 days of administration. The results showed that complete abortion rate was >97%, regardless of type of provider. With regard to safety, the new study results appeared not to reveal any unexpected safety concerns.

The additional clinical safety data for Sunmedabon submitted by the applicant was presented only as a literature reference (e.g. the Lancet study, Warriner 2011) and was not considered sufficient to characterise the safety profile of Sunmedabon. The application was therefore referred to the CMDh.

<u>CMDh referral</u>

During the CMDh procedure, the applicant submitted a full clinical study report of the Sunmedabon study conducted in Nepal that was recently published in the Lancet journal (Warriner et al., 2011). The overall conclusions were that the additional safety data provided in the Warriner study report did not reveal any unexpected adverse events and the results were quite comparable to reports from other studies on medical abortion using similar regimens. The study was reasonably large, appears to have been well conducted and had a low rate of patients lost to follow-up. With regard to the difference in exposure of misoprostol between the pivotal trial and the Warriner trial, there was little in the full study

report to suggest that the higher exposure in the Warriner trial resulted in any clinically relevant negative effects on the safety pattern. This conclusion was endorsed by all CMS.

Furthermore, the requested study protocol of the proposed post-marketing study addressing efficacy and safety was included and was found acceptable.

IV.6 Discussion on the clinical aspects

As stated above, the development of a combined product delivering both components necessary for medical abortion (i.e. mifepristone and misoprostol) is endorsed as it constitutes a measure to reduce the current widespread off-label use of a non-authorized misoprostol product, which is used vaginally although the product is intended for oral use, resulting in unpredictable doses and lack of pharmacovigilance activities.

The current application concerns a formulation of misoprostol that is not entirely comparable to that used in the pivotal and supportive clinical trials as it results in a 70% increased rate and extent of absorption. It should be noted that this is not a generic or a hybrid application, hence demonstration of strict bioequivalence is not expected, nor requested.

The MAH provided arguments for accepting the higher exposure of misoprostol in Sunmedabon compared with Cytotec administered vaginally. This was based partly on data from the pivotal study (i.e. the group receiving additional doses of oral misoprostol after the vaginal dose) and partly on publications using sublingual administration of misoprostol resulting in considerably higher exposure than vaginal administration.

A new published study (Warriner et al., 2011) was also submitted, in which Sunmedabon (same product as in the current application) was given to >1000 pregnant women with gestational duration of <63 days. The efficacy reported as complete abortion rate without surgical intervention as assessed 30 days after administration of drugs in the new study was 96,7%, confirming previous efficacy results from the pivotal study and other published studies. The rate of reported adverse events was in general lower than is usually reported in association to medical abortion using a regimen of 200 mg mifepristone orally and 0,8 mg misoprostol vaginally, which could be a consequence of how adverse event reporting was done, which is not entirely clear in the publication.

The application was referred to the CMDh and following assessment of the full study report for the Warriner (Nepal) study, it was concluded that Sunmedabon has an acceptably high efficacy rate and a side effect and bleeding pattern that is comparable with other studies using similar regimens and a very low rate of serious adverse events.

V. USER CONSULTATION

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Medabon is recommended for approval.

Following a discussion in CMDh, it was concluded that Medabon has an acceptably high efficacy rate and a side effect and bleeding pattern that is comparable with other studies using similar regimens and a very low rate of serious adverse events.

The decentralised procedure for Sunmedabon was successfully finalised on 22 March 2012.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4796/001/IB/016	To adapt RMP in line with PSUSA outcome	No	31-1-2020	Approved	N/A
NL/H/4796/001/P/001	PL update	Yes	21-4-2020	Approved	N/A
NL/H/4796/001/IB/017	Minor changes to the dissolution test procedure for the finished product	No	29-6-2020	Approved	N/A
NL/H/4796/001/IA/018	Add a manufacturer responsible for batch release in the EEA, not including batch control/testing.	Yes	24-8-2020	Approved	N/A
NL/H/4796/001/II/019	To update the ASMF of Misoprostol	No	9-5-2021	Approved	N/A
NL/H/4796/001/IB/020	To update SmPC and PL as a consequence of the PRAC Assessment Report on the PSUR(s) for misoprostol	Yes	19-8-2021	Approved	N/A
NL/H/4796/001/IB/021	To update RMP from V5.2 to V5.3	Yes	19-8-2021	Approved	N/A
NL/H/4796/001/IA/022	To update the Product Information, as a consequence of the PRAC Assessment Report on the PSUR(s) for mifepristone	Yes	26-7-2021	Approved	N/A
NL/H/4796/001/IB/023	Extension of the shelf-life from 21 months to 24 months	Yes	17-1-2022	Approved	N/A
NL/H/4796/001/IB/024	To add an alternative supplier	No	31-3-2022	Approved	N/A
NL/H/4796/001/IA/025/G	To change the dimensions of the blister package of the finished product	No	13-5-2022	Approved	N/A