EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/364824/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hemoprostol

International non-proprietary name: MISOPROSTOL

Procedure No. EMEA/H/W/002652/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
AMTSL	Active management of the third stage of labour
CHMP	Committee for medicinal products for human use
CHN	Community Health Nurse
CHO	Chinese hamster ovary
CMACE	Centre for Maternal and Child Enquiries
DCP	Decentralised Procedure
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
ED50	Dose giving 50% effect
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FIGO	International federation of gynaecology and obstetrics
Hb	Haemoglobin
kg	Kilogram
LD50	Lethal dose for 50% of animals
LHV	Lady Health Visitor
MAA	marketing authorisation application
mg	Milligram
mL	Millilitre
ng	Nanogram
nm	Nanometer
NOAEL	No observed adverse effect level
NSAIDs	Non steroidal anti-inflammatory drugs
PGE	Prostaglandin E
PGF	Prostaglandin F
PPH	Post-partum haemorrhage

PRAC	Pharmacovigilance Risk Assessment Committee
RCT	Randomised clinical trial
SmPC	Summary of Product Characteristics
TBA	Traditional Birth Attendant
µg / mcg	Microgram
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Linepharma France submitted on 28 June 2012 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Hemoprostol.

The eligibility by the World Health Organisation was agreed-upon on 21 December 2011 and eligibility to the centralised procedure confirmed by CHMP on 19 January 2012.

Hemoprostol will exclusively be intended for markets outside the Community.

The applicant applied for the following indication (indication at time of initial submission):

HEMOPROSTOL 200 microgram tablets is indicated in adults of childbearing age for treatment and prevention of Post Partum Haemorrhage.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application, by analogy to the European Legislation-

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

New active Substance status

Not Applicable.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Hemoprostol was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 28 June 2012.
- The procedure started on 15 August 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 30 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 2 November 2012.
- During the meeting on 13 December 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 December 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 May 2013.
- PRAC RMP Advice and assessment overview was adopted by PRAC on 20 May 2013
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 September 2013.
- PRAC RMP Advice and assessment overview was adopted by PRAC on 10 October 2013
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 November 2013.
- PRAC RMP Advice and assessment overview was adopted by PRAC on 05 December 2013
- During the CHMP meeting on 17 December 2013, an oral explanation before the CHMP was cancelled. On 18 December a third Day 180 Overview was circulated.
- During the meeting of January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Hemoprostol on 23 January 2014.

2. Scientific discussion

2.1. Introduction

Problem statement

Hemoprostol contains 200 microgram of the active substance misoprostol, a synthetic analogue of prostaglandin E1, whose main pharmacodynamic property in the reproductive tract is increasing the uterine contractility. Among other effects, misoprostol inhibits the acid gastric secretion and increases the digestive peristaltism.

This application is submitted to the EMA under the legal basis of Article 58 of Regulation (EC) No. 726/2004. The dossier is considered composition wise to be a "full dossier" according to Art 8(3) to Directive 2001/83/EEC, by analogy. Hemoprostol is a medicinal product for human use containing misoprostol (INN). This medicinal product is intended exclusively for markets outside the European Union.

An Article 58 CHMP scientific opinion is an opinion issued by the CHMP, the scientific committee of the EMA, in collaboration with World Health Organisation (WHO). This opinion is based on the evaluation of an application containing data on the quality, safety and efficacy of the product, and concludes on the benefit-risk ratio.

This Article 58 application was submitted for assessment of the benefit-risk ratio of Hemoprostol in the indication (as initially proposed by the applicant) *"treatment and prevention of Post Partum Haemorrhage".*

Though all information regarding the indication "prevention of post partum Haemorrhage" is discussed in this assessment report, this indication has been withdrawn by the applicant during the 2nd Day 180 LoOI of the procedure.

The gold standard for prevention and treatment of Post Partum Haemorrhage (PPH) associated with uterine atony is oxytocin. However, in low resource countries oxytocin is not always available (oxytocin requires cool storage conditions) or feasible (requires IV administration).

About the product

Hemoprostol is presented as oral tablets of misoprostol of 200 micrograms strength for sublingual administration in *treatment* of Post Partum Haemorrhage. It was initially also proposed by the applicant for oral administration in *prevention* of Post Partum Haemorrhage. The part of the indication "prevention of PPH "was withdrawn by the Applicant during the procedure. A summary of the information regarding this part of the indication is therefore discussed in this report, but not in the overall benefit risk assessment.

The approved indication is: *"Hemoprostol is indicated in women of childbearing age for treatment of Post Partum Haemorrhage due to uterine atony in situations where intravenous oxytocin is not available*."

The proposed posology, which was agreed by the CHMP for treatment of Post Partum Haemorrhage is as follows: "*The treatment consists of four tablets (800 micrograms) to be taken*

in a single sublingual intake. The four tablets of HEMOPROSTOL should be placed under the tongue and allowed to melt for 20 minutes."

For prevention of PPH, the applicant had proposed a posology of three tablets (600 micrograms) taken in a single oral intake.

The mechanism of action, as stated in section 5.1 of the SmPC is: "At the recommended dosage, misoprostol induces contractions of the smooth muscle fibres in the myometrium and relaxation of the uterine cervix".

- **Misoprostol medicinal products in other indications :**

The currently approved misoprostol containing medicinal products in Europe are:

- Cytotec®:

Cytotec is approved a.o. in the Netherlands and UK for the prevention of duodenal ulcer and gastric ulcer induced by nonsteroidal anti-inflammatory drugs (NSAID) in arthritic patients at risk, whilst continuing their NSAID therapy.

- Gymiso® (France):

    1. Medical termination of early pregnancy of less than 49 days of amenorrhea, in combination with mifepristone
    2. Preparation of the cervix for surgical termination of pregnancy in the first trimester.

In 2012, an oral tablet of misoprostol 400 mcg (MisoOne) was approved in the EU through DCP for the same indication as accepted for Gymiso: Medical termination of developing intra-uterine pregnancy, in sequential use with mifepristone, up to 49 days of amenorrhea".

- **Background post partum haemorrhage**

According to the WHO, PPH is defined as bleeding from the uterusof 500 ml or more within the first 24 hours of birth of the baby (WHO 2000). This definition is hampered by the extreme difficulty to accurately estimate blood loss in clinical practice (Rath 2011; Yoong 2010). Meticulous estimation of blood loss is not convenient or practicable outside controlled trial settings since blood is often mixed with uncertain amounts of amniotic fluid and dispersed in perineal pads, towels and linens. Besides, the clinical value of a timely diagnosis of PPH through accurate quantification of blood loss is yet to be determined (WHO 2007).

The cut-off of 500 ml has also been criticised on the basis of the clinical relevance of postpartum blood loss of 500 ml in women with normal haemoglobin (Hb) levels before birth (Bloomfield 1990). Consequently, higher cut-off levels have been proposed and these include 600 ml (Beischer 1986), 1000 ml (Burchell 1980) and 1500 ml (Mousa 2002). There is a general agreement that postpartum blood loss in excess of 1000 ml should be regarded as severe PPH. For most deliveries, visual assessment of blood loss is the norm, resulting in many cases of PPH remaining undetected and accurate determination of its incidence difficult. Apart from this 'quantitative' definition of PPH, it can also be qualitatively defined as any degree of post partum

blood loss that is enough to compromise a woman's haemodynamic condition. This definition is more relevant in low-resource settings where the pre-delivery Hb profile of many women is poor.

A systematic review of the prevalence of PPH, using 120 data sets and involving close to four million women, showed an overall prevalence of 6% of all deliveries (Carroli 2008). However, those studies that measured blood loss objectively, as opposed to subjectively, showed higher prevalence. The prevalence also depends on whether the data were derived from observational studies or clinical trials. Higher prevalence was observed in randomised clinical trial settings where meticulous estimation of blood loss is expected.

The risk of maternal death from PPH in developing countries is estimated to be one in 1000 deliveries compared with developed countries such as the UK, where the risk is estimated to be less than one in 100,000 deliveries (CMACE 2011).

Possible aetiologies for PPH are uterine atony, retention of placental tissues, genital tract lacerations (cervix, vagina, vulva), uterine rupture, uterine inversion, coagulation disturbances. Uterine atony (failure of the uterus to contract properly after childbirth) is the leading cause of PPH. Predisposing factors for atony are overstretching of the uterus (e.g. polyhydramnion, multiple gestations), weakness in uterine contractions during labour, macrosomy, grande multiparity, chorioamnionitis, after fundus expression and the use of uterine relaxants.

For **medicinal treatment of post partum haemorrhage** caused by uterine atony, possible options are:

- Oxytocin (Syntocinon®) 5 IE intravenous or intramuscular administration
- Methylergotamine (Methergin®) 0.2 mg intravenous or intramuscular administration
- Sulproston (Nalador®) prostaglandin E2 analogue 500 mcg max intravenously over a period of at least 30 minutes [second line indication (when oxytocin has insufficient effect) in the Netherlands].

Oxytocin is considered the "gold-standard" treatment for post-partum haemorrhage, and has superior efficacy in comparison to methylergotamine, sulproston (PGE2) and misoprostol (PGE1). Misoprostol has been proposed in public literature and guidelines (WHO) as a low-cost, easy-to-use alternative in places where oxytocin is not available (oxytocin requires cool storage conditions) or IV administration is not feasible; however the optimum dose and optimum route of administration have not been established.

Prevention of Post Partum Haemorrhage

Internationally, the WHO recommendations with regard to active management of the third stage of labour (AMTSL) which includes the prophylactic administration of oxytocin is in guidelines in a number of Western countries, among others US, Canada, UK (RCOG guideline). The FIGO (international federation of gynaecology and obstetrics) has started the "Misoprostol for PPH in Low Resource Settings Initiative."

The WHO recommendation is also followed in e.g. the Netherlands, where in the 2nd line (hospitals) prevention of PPH is implemented in the active management of the third stage of labour (AMTSL). This strategy is composed of administration of oxytocin, quick umbilical cord clamping, and controlled cord traction. In the 1st line, this approach is not routine management.

Current opinion in public literature:

The Cochrane review on prostaglandins for preventing postpartum haemorrhage[1] concludes that "misoprostol orally or sublingually at a dose of 600 mcg shows promising results when compared to placebo in reducing blood loss after delivery. The margin of benefit may be affected by whether other components of management of the third stage of labour are used or not. As side-effects are dose-related, research should be directed towards establishing the lowest effective dose for routine use, and the optimal route of administration. However, misoprostol is not preferable to conventional injectable uterotonics as part of the management of the third stage of labour especially for low-risk women."

WHO guidance 2007:

The WHO recommends that **Active management of the third stage of labour (AMTSL) be offered to all women delivering with a *skilled* birth attendant**. Skilled attendants are health professionals who have been educated and trained to proficiency in skills needed to manage normal labour and delivery, recognize the onset of complications, perform essential interventions, start treatment and supervise the referral of mother and baby for interventions that are beyond their competence or are not possible in the particular setting. Depending on the setting, health-care providers such as auxiliary nurse-midwives, community midwives, village midwives and health visitors may also have acquired appropriate skills, if they have been specially trained.

The recommendation that oxytocin should be used by skilled attendants should not prevent attendants who are skilled in administering uterotonics (but not skilled in active management) from using the drug. This is also applicable to misoprostol. However, because of the potential side effects, the WHO indicated that training and experience in the use of the drug is mandatory. Misoprostol has undesirable side effects that are dose related. A dose of 400 mcg has been shown to be effective in preventing PPH but most trials have used 600 mcg because the largest trial by WHO has used that dosage. It may be prudent to use the lowest effective dose to avoid undesirable side effects but this has to be determined based on further trials. Future research should focus on what dose and route of administration of misoprostol are preferred for the best risk-benefit ratio in active management (AMTSL), but also in expectant management (no AMTSL).

WHO 2012[2]:

Recommendation status of the individual components of the active management of the third stage of labour has been changed. The intrinsic contribution of each component of the 'active management of the third stage of labour' was examined in light of new available evidence. All women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH; oxytocin (IM/IV, 10 IU) is the uterotonic of choice. Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is unavailable. Controlled cord traction (CCT) is now optional in settings

[1] Gülmezoglu AM, Forna F, Villar J,Hofmeyr GJ. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD000494. DOI: 10.1002/14651858.CD000494.pub3.

[2] WHO recommendations for the prevention and treatment of postpartum haemorrhage.World Health Organization 2012

where skilled birth attendants are available, but contraindicated in settings where skilled attendants do not assist with births.

Early cord clamping is generally contraindicated and continuous uterine massage is not recommended when prophylactic oxytocin is given, though surveillance of uterine tonus through abdominal palpation is recommended for early identification of postpartum uterine atony.

In summary, in these new recommendations (2012) the WHO considers the use of uterotonics as the main intervention within the whole AMTSL package. Within this context, in settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 µg PO) by community health care workers and lay health workers is recommended for the prevention of PPH.

Advance community distribution of misoprostol for preventing or treating PPH:

In public literature it is under discussion that advance distribution might be a strategy to expand uterotonic coverage to places where conventional uterotonic use, i.e. oxytocin, is not feasible. However, the value and safety of this strategy remains contentious. Current opinion in public literature (Cochrane 2012)[3]: "There is no evidence from randomised or quasi-randomised trials on the benefits or risks of a strategy of advance misoprostol distribution for PPH prevention or treatment in non-facility births. In view of the increasing interest to scale up this strategy, there is an urgent need for large and well-designed randomised trials to evaluate its comparative benefits and risks."

According to WHO 2012 guidance, systematic advanced provision necessitates additional research and cannot be recommended.

Type of Application and aspects on development

This application for Hemoprostol is submitted to the EMA under the legal basis of Article 58 of Regulation (EC) No. 726/2004. The dossier is considered composition wise to be a "full dossier" according to Art 8(3) to Directive 2001/83/EEC by analogy.

Since April 2004 Laboratoire HRA Pharma has marketed misoprostol 200mcg oral tablet in France as Gymiso®. In 2011, the company Linepharma has licensed-in the worldwide rights on Gymiso® from Laboratoire HRA Pharma and currently commercializes Gymiso® in France.

Linepharma France now seeks a CHMP scientific opinion under Article 58 of Regulation No. (EC) 726/2004 for its misoprostol 200mcg tablet in the indication PPH for non-EU countries. The company had provided its tablets to several organizations undertaking clinical development of misoprostol for PPH treatment and prevention and the studies submitted in the present application (study reports HMP061201; HMP061202; HMP061203) have been performed using Linepharma's misoprostol tablet. For clarity, in the present application, studies performed with Gymiso in this dossier are referred to as studies performed with Gymiso / Hemoprostol.

[3] Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. Cochrane Database of Systematic Reviews 2012, Issue 2. Art.No.:CD009336.DOI: 0.1002 / 14651858. CD009336.pub2.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release uncoated tablets containing 200 micrograms of misoprostol as active substance.

Other ingredients are: hypromellose, microcrystalline cellulose, sodium starch glycollate (Type A) and hydrogenated castor oil.

The product is available in dual-face aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The chemical name of misoprostol is mixture of methyl 7-[(1RS,2RS,3RS)-3-hydroxy-2-[(1E,4RS)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1RS, 2RS,3RS)-3-hydroxy-2-[(1E,4SR)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate.

Misoprostol is a clear, colourless or yellowish, oily liquid. It is practically insoluble in water, soluble in ethanol 96% and sparingly soluble in acetonitrile.

Misoprostol exhibits stereoisomerism due to the presence of four chiral centres; the presence of 16 enantiomers is thus possible. Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.

Due to its oily nature misoprostol is very unstable therefore following synthesis misoprostol is stabilised on site by the same manufacturer in a 1% hypromellose dispersion. This dispersion is considered as a drug product intermediate.

Misoprostol is the subject of a monograph in the European Pharmacopeia.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Misoprostol is synthesised in several synthetic steps after which they it is conjugated and purified. The starting materials used are commercially available, well defined and with acceptable specifications. The active substance is manufactured by one manufacturer.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory

Specification

The active substance specification includes tests for appearance (visual examination), identity (IR), assay (Eur. Ph.), impurities (Eur. Ph.), residual solvents (GC), water content (Eur. Ph.) and heavy metals (Eur. Ph.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and heavy metals. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis data on three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on four primary batches and two production scale batches of active substance from the proposed manufacturer stored in the intended commercial package were provided. Three batches were placed under long term conditions (at -15 °C or -20°C ± 5°C/ ambient humidity) for up to 12 months. In addition, three batches were placed under accelerated conditions (at 5 °C ± 3°C/ambient humidity) for up to 6 months.

The following parameters were tested: appearance, assay, water and impurities. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Misoprostol, as described in the Ph. Eur., is an oily liquid which is very unstable and difficult to be process into a drug product in liquid form. The stability of misoprostol is significantly enhanced when it is dispersed in hypromellose. Hence, misoprostol dispersed in hypromellose is used as an intermediate in the manufacture of misoprostol tablets. The dispersion consists of a powder that can be stored at 5±3 °C, whereas the actual active substance is an oily liquid that needs to be stored at -20°C.

Although misoprostol is sensitive to water, when the water content in the dispersion is below 2%, the rate of misoprostol degradation is found to be minimal. As microcrystalline cellulose is the main excipient of the finished product and misoprostol is sensitive to water, the specification of the loss on drying of this excipient is stricter than in the Eur. Ph. monograph.

The proposed formulation of misoprostol tablets is based on Cytotec® (Hemoprostol 200 micrograms tablets). The finished product, initially developed for oral use, is to be used as single sublingual dose of four tablets to be taken over a time period of 20 minutes, for the treatment of post-partum haemorrhage. The sublingual route of administration is supported by clinical studies. The timely release of the active substance is controlled by tight specifications for disintegration and dissolution that are suitable for the sublingual route. The proposed release methods have demonstrated to sufficiently ensure adequate release of the active substance by both oral and sublingual route. The discriminatory power of the dissolution method has been demonstrated.

The formulation used during clinical studies is the same as that used for marketing.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation.

The excipients used in misoprostol tablets are qualitatively identical and quantitatively similar to those used in Cytotec. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The product is packed in dual face aluminum blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process of the 1% dispersion of misoprostol in hypromellose and its specification are described in the literature.

Due to particular sensitivity of misoprostol to water, the manufacture of the tablets takes place in a low relative humidity area.

The manufacturing process is considered as non-standard as the active substance is present in a concentration of less than 2%. The process is a direct compression method that consists of four steps, two blending steps followed by lubrication and tableting. The powder obtained after the mixing steps is dried again to produce the product intermediate, the 1% dispersion with hypromellose. The mixing steps can be considered as critical steps because the content uniformity of the tablets depends directly on the homogeneity of the final blend.

Process validation has been provided for three full scale batches. The homogeneity of the final blend is adequately validated.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for direct compression of immediate release tablets.

Product specification

The finished product release specification contains appropriate tests for this kind of dosage form which include: appearance (visual), identification (HPLC), assay (HPLC), content uniformity (Ph. Eur), hardness (Ph. Eur), friability (Ph. Eur), water content Ph. Eur), disintegration (Ph. Eur), dissolution (Ph. Eur), microbial contamination (Ph. Eur) and related substances (HPLC).

Batch analysis results are provided for two industrial scale validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data for two full scale batches of finished product stored for up to 24 months and for up to 9 months for a third one under long term conditions at 25 ºC / 60% RH, and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (visual), identification (HPLC), assay (HPLC), water content (Ph.Eur), disintegration (Ph.Eur), dissolution (Ph.Eur), microbial contamination (Ph.Eur) and related substances (HPLC). The analytical procedures used are stability indicating.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

The studies described in this dossier have been performed before 1985. Therefore they are not performed according to GLP regulations as this was only introduced in 1987. However, they were published in a peer-reviewed journal and are of sufficient quality.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Misoprostol is a PGE1 analogue that binds to prostanoid receptors, with highest affinity for the EP3 and EP4 receptor. The mechanism of action has been tested in vitro (ex vivo), on human myometrium samples from pregnant and non-pregnant women. Misoprostol showed a biphasic response on the myometrium, whether pregnant or nonpregnant, with stimulation of contraction at lower concentrations and inhibition of contraction at higher concentrations. It is suggested that the relaxation of human non-pregnant myometrium is by an EP2-receptor mediated process. In vivo effects in women are discussed in the clinical AR.

Secondary pharmacodynamic studies

Various studies have shown both contraction and relaxation effects of misoprostol on various tissue preparations.

Misoprostol reduces gastric acid secretion in rats and dogs. The volume of the secretion as well as the hydrogen ion concentration was reduced. This well established action of misoprostol is considered to be a secondary pharmacological effect for the current application.

Safety pharmacology programme

The safety pharmacology section of the dossier is based on a single review of the original data produced for misoprostol. In the mouse, doses of up to 0.32 mg/kg had no effect on the central nervous system. At a high dose of 4.5 mg/kg administered i.p., sedation was observed; however, this is not likely to be clinically relevant.

No effects on cardiovascular parameters were seen at doses up to 30 µg/kg in dogs. Since the studies described are quite old, no state of the art in vitro studies were performed. This is considered acceptable considering the lack of cardiovascular effects in vivo and in the clinic. The main effect of misoprostol in inducing diarrhoea in mice and rats in gastrointestinal studies is known to be clinically relevant.

Pharmacodynamic drug interactions

The non-clinical and clinical data provided, suggest that the potential for interaction at secondary targets or effects on the cardiovascular, respiratory, central nervous and renal systems are low when the product is administered orally at up to 800 µg/day. The proposed dose of Hemoprostol for oral use is within the range of that used previously. However, it is noted that the proposed route of administration is 800 µg/day sublingually. The Applicant has performed a pharmacokinetic study in healthy female volunteers and the data demonstrate that the Cmax following sublingual administration at 800 µg is comparable to that observed following oral administration. The AUC following sublingual administration was slightly higher than that associated with oral administration; however the observed difference was <2-fold.

On the basis of these data it is agreed that the potential for interaction at secondary targets or effects on the core organ systems following sublingual administration is comparable to that observed when the product is administered orally, as observed with the current clinical use of Gymiso® or Cytotec®.

2.3.3. Pharmacokinetics

A brief overview of data on pharmacokinetic properties of misoprostol is provided. Misoprostol was rapidly de-esterified to its free acid, SC-30695, following absorption in all species and plasma levels were thus followed by measuring levels of radioactivity. Absorption was rapid in all species, including man, with similar maximum plasma levels in dog and man after a dose of 0.002 mg/kg (approximately 2 to 2.5 ng/mL). However, in rats a peak level of approximately 360 ng/mL was reached for a dose of 1 mg/kg, which, assuming linearity, would give a level of 0.7 ng/mL for a dose of 0.002 mg/kg. Absorption of total radioactivity was almost complete in mouse (84% from urinary data), rat (85% from urinary data), dog (100% from plasma data) and in man (64-73% from urinary data).

Distribution studies in the rat using [17,18-3H]-misoprostol showed tissue to plasma ratios of radioactivity of 6 to 73 for the large and small intestine, stomach, liver and kidney; the tissue to plasma ratio for all other tissues examined was less than unity. Clearance of radioactivity was essentially complete within 24 hours with remaining radioactivity attributable to tritiated water. Serum protein binding of labeled SC-30695 was studied in man and was similar in young (81-88%) and elderly (81-89%) subjects. Accumulation in erythrocytes was not seen.

Metabolism of misoprostol to the free acid, SC-30695, was rapid with no intact misoprostol found in plasma samples from man - consistent with an *in vitro* half-life of 6.4 minutes for de-esterification of misoprostol in human plasma at 37ºC. The free acid was then further metabolized to more polar compounds in the rat, dog and monkey. The pharmacological inactive dinor and tetranor metabolites of SC-30695 were isolated and identified in human urine. In all species examined, misoprostol acid was metabolized to inactive metabolites by beta oxidation of the alpha chain, omega oxidation of the beta chain, and to F prostaglandin analogues. Limited studies on effects of misoprostol on hepatic drug metabolism in the rat did not show any effect on aminopyrine metabolism (single oral dose of 0.1 mg/kg of misoprostol) or, after 0.1 mg/kg

twice daily for four days, on cytochrome P450 content or the activities in liver microsomes of hexobarbital hydroxylase, aniline hydrolase or p-nitroanisole O-demethylase.

Elimination of radioactivity of parent compound and its metabolites was rapid with a plasma elimination half-life of 3H-SC-30695 of 21 minutes in man. Data on elimination of radioactivity was confounded by the formation of tritiated water from the [17,18-3H]-misoprostol used in these studies. The terminal half-lives of SC-30695 and several other drug-related metabolites, i.e. excluding tritiated water, were 4.5 hours or less in rat, dog and monkey. The majority of metabolites is excreted in the urine (30-63%) rather than in the faeces (21-48%). Misoprostol is excreted into human breast milk, with maximum concentrations reached at one hour after dosing.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed with doses far above clinically relevant doses. The most prominent clinical signs were diarrhoea and reduced motor activity in rodents and, in dogs, emesis, tremors, mydriasis and diarrhoea, of which diarrhoea is likely to be the only clinically relevant effect. LD50 values were around 80-90 mg/kg in rats and 120-130 mg/kg in mice after oral dosing.

Repeat dose toxicity

Repeated dose toxicity studies were performed in rats and dogs for up to 52 weeks. In rats, the major clinical signs were diarrhoea, salivation, vaginal dilation and discharge, decreased body weight (mainly males) and increased food consumption. There was no effect on rectal temperature in the 5 week study in which this parameter was monitored. Decreases in serum total protein were seen at high doses and probably due to poor absorption due to diarrhoea. Increases in serum iron seen at high doses remain unexplained. These changes are unlikely to be of clinical relevance due to the extended and high dosing, as compared to the human situation. Hyperkeratosis and hyperplasia of the stomach, seen in both rats and dogs, is probably due to the pharmacological action of inhibition of gastric acid secretion. In dogs the most important clinical signs were emesis, diarrhoea, soft and/or mucoid stools and increased rectal temperature. Diarrhoea and increased temperature are known clinical adverse effects of misoprostol treatment. Serum chloride levels were increased, but only after 52 weeks of treatment, and therefore unlikely to be clinically relevant.

Data in the literature do not clearly define exposures at the no-effect levels for the repeated-dose studies, however these doses are 2-24 fold higher than clinical doses based on mg/kg. Moreover, clinical use following oral administration of misoprostol is well established and the exposures observed following sublingual administration are comparable to that observed following oral administration.

Genotoxicity

Misoprostol is not genotoxic, based on a standard battery of genotoxicity tests.

Carcinogenicity

Misoprostol is not carcinogenic in rats and mice, following repeated administration for 24 and 21 months, respectively.

Reproduction Toxicity

In fertility studies in rats, there was an increase in the number of resorptions at high doses. The NOAEL for this effect was 400 µg/kg/day, which is far above the single dose of 13 µg/kg in women.

Misoprostol was not teratogenic in rats and rabbits up to 10000 µg/kg/day and 1000 µg/kg/day, respectively. Increased resorptions and decreased implantations have been observed in the rat and the rabbit, at doses that are substantially higher than those proposed clinically. These findings are not considered to be relevant if used as proposed, as the product is to be administered via a single application post partum.

There was no clinically relevant effect on pre- and postnatal development in rats. Clinical data indicate a risk of malformations in case of exposure to misoprostol during pregnancy. This is a recognized risk, and although it is agreed that this risk is not relevant for the indication applied for, the relevant warnings (as outlined in the SmPC for Cytotec) which describe the risks for potential malformations/birth defects have been included in Section 4.6 of the SmPC.

Toxicokinetic data

Not applicable

Local Tolerance

No nonclinical data on local tolerance were submitted; this is acceptable in view of the experience accumulated on local tolerance after oral administration of misoprostol in other indications.

2.3.5. Ecotoxicity / environmental risk assessment

An environmental risk assessment (ERA) is not required for applications under Article 58 of Regulation (EC) No 726/2004.

2.3.6. Discussion on non-clinical aspects

The non-clinical data submitted fulfil the requirements of an application submitted under Article 58 of Regulation (EC) No. 726/2004. These data refer in particular to the primary pharmacodynamics and toxicology of misoprostol. With regard to the pharmacokinetics of misoprostol, the non-clinical data are limited. However, in light of the available clinical data, this is considered acceptable.

It is noted that clinical data indicate a risk of malformations due to exposure to misoprostol during pregnancy. This is a recognized risk, and although it is agreed that this risk is not relevant for the proposed indication, the relevant warnings (as outlined in the SmPC for Cytotec) which describe the risks for potential malformations/birth defects have been included within Section 4.6 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers that non-clinical issues have been addressed satisfactorily.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program consists of 2 published Phase III studies in the treatment of post partum haemorrhage and 1 published phase III study in the prevention of post partum haemorrhage.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Absorption

When administered orally, misoprostol, an ester, is rapidly and completely de-esterified to pharmacologically active carboxylic acid in the stomach. Absorption of misoprostolic acid is rapid, with peak plasma concentration in 15-30 minutes. A 200 mcg oral dose produces a peak plasma concentration of the acid metabolite of 309 ng/L. The acid has a plasma half-life of 13 - 40 minutes. No detectable concentrations of the parent ester can be found in plasma, and only approximately 7% of the dose is systematically bioavailable as the acid after oral administration.

After administration by the sublingual route, the absorption is delayed and the extent of absorption increased by 60% in comparison with the oral administration.

Concomitant ingestion of food decreases the bioavailability of oral misoprostol. However, due to the need for urgent administration after infant delivery, it is agreed that HEMOPROSTOL can be taken at any moment.

The applicant undertook a bioequivalence study in order to bridge the toxicology data (performed with Cytotec tablets) with Hemoprostol tablets (which are identical to Gymiso tablets), Study No. JEI308 - Bioequivalence Study of GYMISO® (Misoprostol 200 µg Tablet) Compared to CYTOTEC® (Misoprostol 200 µg Tablet).

This was a randomized, cross-over, double-blinded study performed in 19 healthy female volunteers (aged 21 - 37 years, BMI of 17 - 25 kg/m2) by Protech Pharmaservices Corporation, Taiwan. Subjects had to have a negative pregnancy test result at the beginning of each study period. They received in a randomized order administered with 240 ml water after fasting either Treatment A (reference): a single dose of 2 tablets of CYTOTEC® (each tablet containing 200 µg misoprostol, manufactured by Pharmacia S.A.S, batch n° 115020, actual content 99.1% of declared amount) or Treatment B: a single dose of 2 tablets of GYMISO (each tablet containing 200 µg misoprostol, manufactured by Laboratoire HRA Pharma, batch n° U15691, batch size 100.000 tablets, actual content 100.5% of declared amount).

Blood was sampled 00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.3, 0.4, 1.0, 1.3, 2.0, 3.0, and 4.0 hours after administration. Misoprostol acid was determined in plasma with a validated LC-MS/MS method.

The wash out period between the treatments was at least 1 week.

The following pharmacokinetic parameters of misoprostol acid were, measured as clinical endpoints: Cmax, tmax, AUC0-t, AUC0-∞, t1/2, AUMC, MRT and kel.

Bioequivalence was tested according the current guideline. The results are listed in the table below.

Table 1. Pharmacokinetic parameters of misoprostol acid: non-transformed values; arithmetic mean ± SD)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	0.71 ± 0.25	0.75 ± 0.26	1.10 ± 0.42	0.25 ± 0.13	0.58 ± 0.44
Reference	0.74 ± 0.23	0.77 ± 0.24	1.19 ± 0.46	0.25 ± 0.20	0.53 ± 0.21
***Ratio (90% CI)**	0.95 0.89 - 1.01	0.96+0.90 - 1.02	0.94 0.83 - 1.05		
CV (%)	9.6%	9.4%	23%		

$AUC_{0-\infty}$ 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

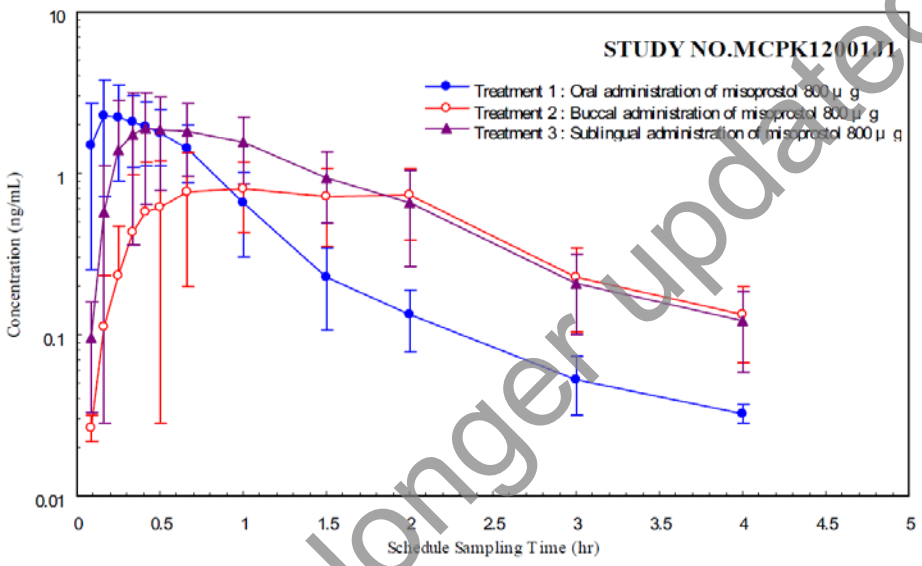
**ln-transformed values*

The results showed that both tablets formulations of misoprostol are considered bioequivalent after oral administration with 240 ml water. As the pharmacokinetics of misoprostol acid are linear and misoprostol can be considered as a Class I drug in the BCS, the lack of a study with the highest dose after oral administration (600 µg) is considered acceptable.

For the indication "Treatment of PPH" the dose will be 800 µg sublingually administered as 4 tablets. The Applicant conducted an additional comparative bioavailability study with 4 tablets of 200 µg administered by the sublingual route in comparison with oral and buccal administration.

In the figure below the plasma concentration-time curves after administration of 4 tablets of 200 µg by the three different routes are given.

Figure 1



Distribution

In both young and elderly subjects, misoprostol acid is 85% bound to serum albumin plasma protein in a concentration-independent fashion. Serum protein binding is reduced in the presence of high salicylic acid concentrations (>100 mcg/ml). It has not been reported whether relative proportions of the stereoisomers in systemic circulation are the same as of different proportions in the tablet.

Elimination

Approximately 80% of radioactivity is recovered in urine after an oral dose of ^{3}H-misoprostol. A negligible amount of the parent compound or misoprostolic acid appears in urine. Misoprostol acid is further metabolized by beta oxidation on the alpha side chain, omega oxidation of the beta-side chain and reduction to prostaglandin F analogs.

2.4.3. Pharmacodynamics

Prostaglandin E2 contracts or relaxes many smooth muscles. Strips of non-pregnant human uterus are relaxed by PGE2; strips from pregnant women are contracted by low concentrations of PGE2 and relaxed by high concentrations. Misoprostol, a prostaglandin E1 analogue, is supposed to share these general properties of Prostaglandin E2.

Mechanism of action

Misoprostol is a synthetic analogue of prostaglandin E1. In the reproductive tract, misoprostol increases the uterine contractility. Among other effects, misoprostol inhibits the acid gastric secretion and increases the digestive peristaltism.

Primary and Secondary pharmacology

The applicant has not performed pharmacodynamic studies, as they considered misoprostol as a known active substance, but refer to public literature. Key reference is the review by Gemzell-Danielsson et al.[4], in women seeking medical abortion, in which studies on uterine contractility following administration of misoprostol via the oral, vaginal or sublingual route were compared. In the reviewed studies, **uterine contractility** was measured in women seeking a medical termination of pregnancy with mifepristone (200 mg) followed by misoprostol. Pressure was recorded prior to and during 4 h following misoprostol administration (figure 2).

Other publications show that an increase in uterine tonus occurred after a significantly shorter time following oral (7.8 min) and sublingual (10.7 – 11.5 min) intake than after vaginal (19.4 min) administration. The time to maximum tonus elevation was also significantly shorter (39.5, 47.1–51.7 and 62.2 min, respectively).[5] Regular uterine contractions developed in all subjects following sublingual and vaginal administration but not after oral administration.

The increase in uterine activity measured in Montevideo Units (MU) was significantly higher after 2 h and thereafter for sublingual and vaginal treatment than for oral misoprostol (Figure 3). The contractility pattern that developed was very similar following vaginal or sublingual administration and was significantly more pronounced than for the oral route.

[4] Gemzell-Danielsson K, Bygdeman M, Aronsson A. Studies on uterine contractility following mifepristone and various routes of misoprostol. Contraception 2006, 74, 31-35
[5] Aronsson et al. Effects of misoprostol on uterine contractility following different routes of administration

Figure 2 Contractility:

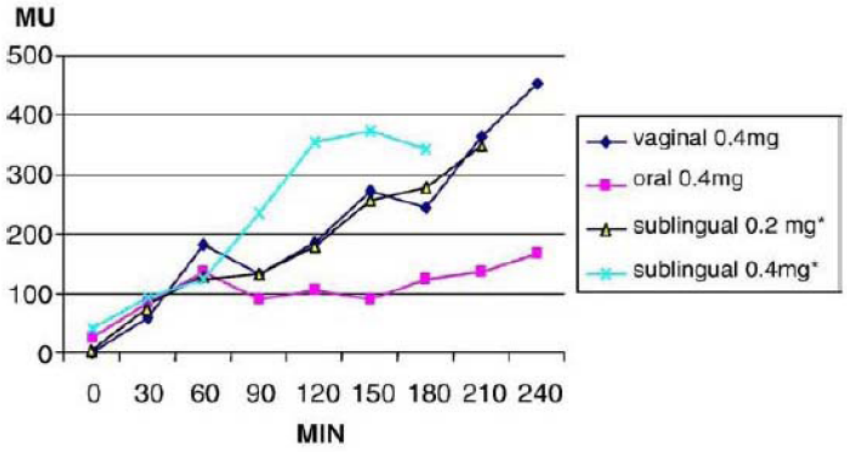
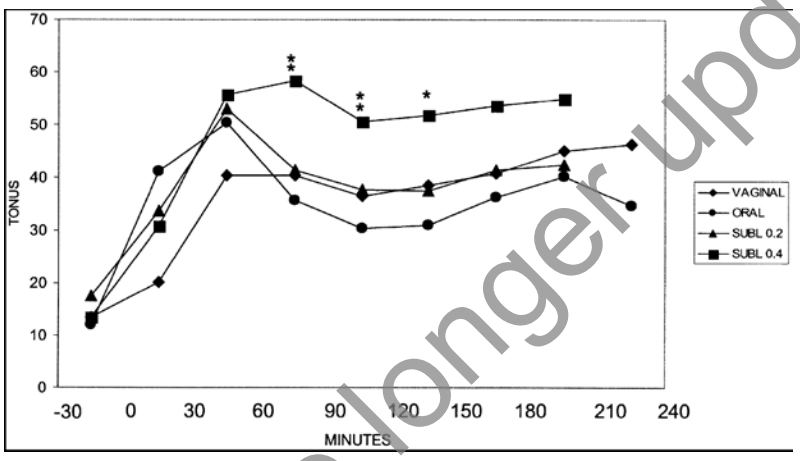


Figure 2.5-4 Effect on uterine contractions (Montevideo Units, MU) after oral, vaginal or sublingual administration of misoprostol (from ref. 910)

Figure 3 Uterine tonus:



Uterine tonus was measured in mmHg. 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) group and the oral group: *P < 0.05, **P < 0.01

Additional information is available from pharmacodynamic studies in women in the postpartum situation. Only few papers have evaluated the effect of misoprostol on uterine pressure immediately post-delivery.

In the work by Chong et al (Eur. J Ob Gyn, 2004), pre and post-treatment uterine activity were measured with intrauterine pressure catheters after spontaneous vaginal delivery in fifty women. They were given either 400 µg misoprostol via the oral (oral solution or oral tablet), rectal or vaginal routes, or 1ml im syntometrine. The following table extracted from the publication summarizes the observed results.

Table 2

Table 2
Mean uterine activity in each 15 min period after treatment

Time after treatment (min)	Mean (95% CI) uterine (kPa s) in 15 min period				
	Intramuscular syntometrine 1 ml	Misoprostol 400 µg oral tablet	Misoprostol 400 µg oral solution	Misoprostol 400 µg rectal	Misoprostol 400 µg vaginal
15	4508 (3293–5723)	2815 (1885–3746)	5468 (4046–6890)	2958 (1644–4273)	1991 (928–3054)
30	4873 (3184 –6561)	4101 (2782–5419)	4905 (3573–6236)	3353 (2048–4658)	2858 (1480–4235)
45	3910 (2532–5287)	3967 (2331–5604)	4494 (3167–5820)	2920 (1845–3996)	2848 (1690–4006)
60	3526 (2252–4799)	3792 (2333–5252)	4242 (3107–5377)	2237 (1195–3280)	2853 (1378–4327)
75	3035 (1853–4216)	2954 (1798–4111)	3816 (2454–5177)	1914 (1182–2646)	2586 (1380–3792)
90	2680 (1778–3581)	2370 (1658–3081)	3432 (2182–4681)	2150 (1263–3037)	2393 (1428–3357)

The difference in time of onset of action among the different groups was highly statistically significant (P < 0:001). Misoprostol given as an aqueous oral solution had a significantly shorter median onset of action (4.0 min, range 2.0–5.0 min) compared to misoprostol given as tablets orally (6.0 min, range 4.0–10.0 min, P < 0:01), rectally (11.0 min, range 7.0–13.0 min, P < 0:001) or vaginally (20.0 min, range 11.0–25.0 min, P < 0:001) (Table 2). The time of onset of action for oral solution misoprostol 400 mg was not significantly different from that of intramuscularly administered syntometrine (2.5 min, range 2.0–6.0 min, P = 0:393). Nevertheless, the outcome of this study confirms that route of administration is important in terms of onset of effect, and degree of uterine activity.

In this study, shivering and pyrexia were recorded in 50% and 90%, respectively, of women given the aqueous oral solution of misoprostol, and were significantly higher than in the women treated with the other forms / routes of misoprostol.

In the study by Elati et al (BJOG 2011), 35 women were randomised to received 200, 400 or 600µg misoprostol sublingually after spontaneous delivery; they were compared to 14 women who received 10 IU of im oxytocin. Intrauterine pressure was measured immediately after placental delivery.

Table 3

Table 1. Basic characteristics of four treatment groups

	Oxytocin 10 IU IM	Sublingual misoprostol		
		200 µg	400 µg	600 µg
No. of women recruited	14	12	12	11
Parity, *n* (%)				
0	2 (14)	0	1 (8.3)	1 (9)
1	4 (28.5)	3 (25)	3 (25)	2 (18)
2	4 (28.5)	5 (41.5)	4 (33.3)	5 (45)
>2	4 (28.5)	4 (28.5)	4 (28.5)	3 (27.3)
Age (years)	28.5 ± 6.2	28 .1 ± 5.4	27 ± 3.3	26.3 ± 3.7
Gestational age (weeks)	40.2 ± 1.4	40.1 ± 1.1	40.3 ± 0.8	41 ± 1.1
Birthweight (g)	3350 ± 0.364	3458 ± 0.262	3595 ± 0.397	3522 ± 0.337

Date are mean ± SD unless otherwise stated.

The following figure, extracted from the publication, summarizes the observed results. There was no difference in intrauterine pressure between the 3 misoprostol doses. The uterine pressure was significantly lower (P < 0.008) with either dose of misoprostol than with oxytocin in the first 10 minutes, whereas it was significantly higher (P < 0.008) with misoprostol than with oxytocin from 50 to 120 minutes. A dose-related rise in body temperature and chills was observed in women given misoprostol. Temperature above 39°C was reported in 8.3, 8.3 and 45% of women given 200, 400 and 600µg misoprostol, respectively.

Figure 4

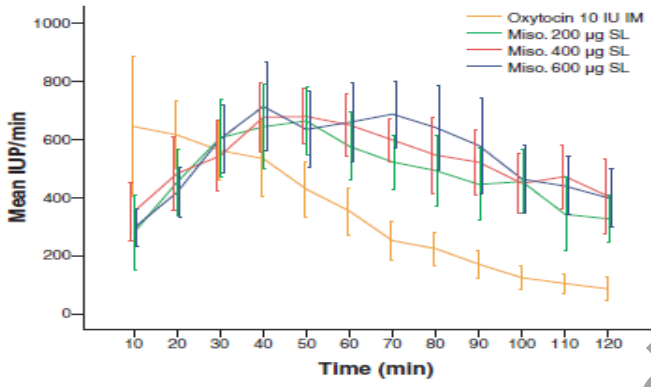


Figure 3. Line graph of mean postpartum uterine pressure in the different treatment groups. Data are presented as Montevideo units (MVU; ±SEM). The data in the first 10 minutes are adjusted to correct for the timing of placental delivery (MVU per minute).

The authors` conclusion in Elati et al was that "intramuscular oxytocin has the highest immediate post partum uterine activity. Lower doses of misoprostol may be as effective as high doses and with fewer side effects. Clinical outcomes with low-dose misoprostol should be further explored."

The reasons for higher activity of non-oral routes are unclear, but could be related to the higher exposure to misoprostol administered via vaginal or sublingual routes than with the oral route. Dose and route of administration selection in current indications are discussed in the clinical section.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of misoprostol acid are well described. The exposure after sublingual administration of 800 µg misoprostol (t_{max}) is delayed in comparison to the oral administration from 0.34 to 0.7 hours resulting in a comparable C_{max} but a 60% higher AUC probably due to the lower first-pass effect after the sublingual route of administration. The results of the PK study did not raise any further safety concerns.

The pharmacodynamic properties of misoprostol on the uterus, i.e. increase in uterine tonus and activity (contractility) are well-known from literature; the one pharmacodynamic review submitted referred to summarized studies performed in relation to the indication of medical abortion and with different dosages. Dose-response data collected post-partum in relation to the current indications and differences between routes of administration, confirm that route of administration is important in terms of onset of effect, and degree of uterine activity (Chong et al). Evaluation of different doses (200, 400, 600 µg) given sublingually immediately postpartum suggested that there was no clear difference in uterine activity between the different misoprostol doses given postpartum (Elati et al). This information could have been taken along in selecting the oral dose of misoprostol to be used prophylactically. However, as the prevention indication has been withdrawn by the applicant during the assessment, this is not an issue.

2.4.5. Conclusions on clinical pharmacology

Bioequivalence of the Hemoprostol (Gymiso /misoprostol 200 µg) with the reference product Cytotec (misoprostol 200 µg) has been established. The extent of exposure (AUC) of the product after sublingual administration increased 60%, as compared to the oral route and the Cmax was comparable.

The pharmacodynamic properties of misoprostol on the uterus, i.e. increase in uterine tonus and activity (contractility) are well-known from literature, but the one pharmacodynamic review referred to summarized studies performed in relation to the indication of medical abortion and with different dosages. Dose-response data collected post-partum in relation to the current indications and differences between routes of administration, indicated that route of administration is important in terms of onset of effect, and degree of uterine activity. Evaluation of different doses (200, 400, 600 mcg) given sublingually immediately postpartum suggested no clear difference in uterine activity between the different doses given.

2.5. Clinical efficacy

The efficacy of misoprostol in the treatment of PPH was assessed in 2 published studies for which the company has supplied misoprostol to the organization sponsoring the studies (Gynuity).

- Treatment of post-partum haemorrhage with sublingual Gymiso / Hemoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial (Study Report HMP061202)

Winikoff B, Dabash R, Durocher J. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non inferiority trial. Lancet 2010 Jan 16; 375(9710): 210-6.

- Treatment of post-partum haemorrhage with sublingual Gymiso / Hemoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial (Study Report HMP061201).

Blum J. Winikoff B. Raghavan S Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. Lancet 2010 Jan 16; 375(9710):217-23.

Both efficacy-safety studies were prospective, randomized, double-blind, multicenter trials. Table 4 summarizes the key design characteristics of the efficacy studies.

Table 4 Design characteristics of the 2 pivotal efficacy studies

Study	design	Treatment duration	Treatment groups	Dose	N	Location
HMP061202	Double-blind, active controlled	Single dose	Misoprostol Oxytocin	800 mcg sublingually	488 490	Ecuador, Egypt Vietnam

				40 IU intravenous		
HMP061201	Double-blind, active controlled	Single dose	Misoprostol Oxytocin	800 mcg Sublingually 40 IU intravenous +prophylactic oxytocin10 IU	407 402	Burkina Faso Turkey Egypt Vietnam

Clinical documentation submitted for prevention of post partum haemorrhage was 1 study:

- Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomized placebo-controlled trial (Study Report HMP061203)

Mobeen N, Durocher J, Zuberi N, Jahan N, Blum J, Wasim S, et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG 2011; 118(3): 353-61.

This efficacy-safety study was a prospective, randomized, double-blind, placebo-controlled community based trial. Table 5 summarizes the key design characteristics of the study.

Table 5 Design characteristics of the pivotal study in prevention of PPH

Study	design	Treatment duration	Treatment groups	Dose	N	Location
HMP061203	Double-blind, placebo-controlled	Single dose	Misoprostol Placebo	600 mcg orally Placebo	534 585	46 villages in Pakistan

2.5.1. Dose response studies in the treatment of post partum haemorrhage

No dose response studies were performed, but the selected dose and route of administration of misoprostol in the indication treatment of PPH are considered sufficiently substantiated. The convenience of sublingual administration of 4 tablets which need to be melted under the tongue for 20 minutes are acceptable, as substantiated by the underlying data collected by the study investigators.

2.5.2. Main study(ies) in the treatment of post partum haemorrhage

Methods

Study participants

Inclusion Criteria:

- Vaginal delivery at the study hospital
- Primary postpartum haemorrhage suspected to be due to uterine atony
- No uterotonic agent administered during the third stage of labour or prior in study HMP061202; Oxytocin administered in the third stage of labour in study HMP061201
- Willingness to participate in the trial and to respond to a short questionnaire

Exclusion Criteria:

- Known allergy to misoprostol or other prostaglandins
- C-section during current delivery
- Administration of a uterotonic during the third stage of labour in study HMP061202
- Induction or augmentation of current labour with any uterotonic in study HMP061202

Women with known allergy to prostaglandins were excluded and women who had a caesarean section during their current delivery were excluded because PPH after caesarean is a fundamentally different clinical situation. Women who received a uterotonic during the third stage of labour or had the current labour induced or augmented were excluded from study HMP061202 because the objective of the study is to assess the efficacy of the two drugs among women who were naïve to uterotonic therapy during labour.

Treatments

Products are given together with a placebo (double-dummy)

Misoprostol: Participants received four 200µg tablets of misoprostol sublingually held under the tongue for 20 minutes and the swallowed if remnants remained) + an IV of saline, resembling oxytocin upon diagnosis of PPH due to suspected uterine atony.

Oxytocin: Participants received 40 IU of oxytocin intravenously (maximum effective dose according to an expert group) in 1000 mL solution administered over a period of 15 minutes + 4 placebo tablets resembling misoprostol sublingually (held under the tongue for 20 minutes and the swallowed if remnants remained) upon diagnosis of PPH due to suspected uterine atony.

In case of continued bleeding: If active bleeding did not stop within 20 min of initial treatment, providers were instructed to give standard care. Providers were asked to restrict any additional misoprostol to 200 µg in view of the little evidence for this procedure and concerns about high fever and shivering after high doses of misoprostol.

Objectives

To determine if misoprostol is as effective as oxytocin for treatment of primary PPH when no oxytocin prophylaxis has been given:

- To determine whether 800 µg sublingual misoprostol is as effective as 40 IU intravenous oxytocin for treatment of primary postpartum haemorrhage among women who have not received prophylactic therapy (study HMP061202)

To determine whether 800 µg sublingual misoprostol is as effective as 40 IU intravenous oxytocin for treatment of primary postpartum haemorrhage when prophylactic therapy with oxytocin has failed. (HMP061201)

- To characterize the safety profile of misoprostol for treatment of postpartum haemorrhage.
- To determine whether the regimen and side effect profile are acceptable to women.
- To determine whether misoprostol can be safely and feasibly incorporated into developing country health care delivery systems for treatment of PPH.

Outcomes/endpoints

Primary efficacy variables were selected based on a review of the literature and convening an expert panel:

- Cessation of active bleeding within 20 minutes of treatment
- Additional blood loss of 300 mL or more after treatment.

Additionally, a list of measurements was to be performed:

- Blood loss was measured using a calibrated drape .

  However, treatment was triggered by diagnosis of primary PPH, which was defined either through visual estimation by the provider or as blood loss ≥ 700 mL using the calibrated drape, whichever occurred first.

  Total blood loss was recorded at time of diagnosis of PPH, at time of treatment, 20 minutes after treatment, and when active bleeding stopped. Doctors and nurses trained in study protocol and in use of the drape were responsible for measuring and recording blood loss.

  This protocol quantitatively measured PPH (defined PPH as 700mL according to the blood measurement container) to allow for an objective measure. Yet it was also allowed for subjective PPH diagnosis based on provider decision to treat at any point—as is standard practice in most settings. Although PPH has traditionally been defined as 500 mL or more of blood loss after completion of the third stage of labor, it is widely recognized that nearly half of all women who delivery vaginally regularly lose ≥ 500 mL of blood in a normal delivery. Therefore, if providers have not diagnosed PPH by the time blood loss

equals 700mL on the measurement container, only at that point will the protocol require them to enroll women and initiate treatment.

- Haemoglobin readings were collected for women prior to delivery and then again prior to discharge using Hemocue hemoglobin machine + cuvette.

Secondary outcomes:

- total blood loss after treatment,
- change in haemoglobin concentration after treatment,
- time to active bleeding cessation,
- any other additional interventions.

Sample size

The studies were designed as non-inferiority trials. Oxytocin was postulated to stop bleeding within 20 minutes for 88% of women. No trials had been previously published on the efficacy of oxytocin; therefore its efficacy as the reference treatment was based on expert opinion. It was proposed that misoprostol would work similarly and that a **6% margin of inferiority** would be acceptable as clinically equivalent in public health terms. Based on these assumptions, for 80% power, α of .05, and a one-sided test, 870 women were needed. An additional 10% were planned to account for protocol violations or loss to follow up for a total of 958 women (479 per study group).

Randomisation

After diagnosis of postpartum hemorrhage, randomization and treatment occurred immediately. Sealed and numbered opaque boxes contained the treatment allocation and were opened in strict numeric sequence. A computer-generated random allocation sequence in blocks of ten was derived by Gynuity Health Projects in New York, USA and was not revealed until data collection and cleaning were completed.

Blinding (masking)

Products are given together with a placebo (double-blind and double-dummy) as explained in the *section on Treatments.*

Prior and Concomitant Therapy

HMP061202:

To comply with eligibility requirements, all participants should not have received an uterotonic drug during the third stage of labour, nor could they have received a uterotonic for induction or augmentation of labour. Case report forms specifically asked for listing of any prior or concomitant therapy. Study protocols required that if active bleeding did not stop after 20 minutes then the standard of care was followed.

HMP061201:

To comply with eligibility requirements, all participants must have received oxytocin prophylaxis during the third stage of labour. If oxytocin was used for induction or augmentation of labor, it was clearly recorded on the case report forms. Case report forms specifically asked for listing of any prior or concomitant therapy. Study protocols required that if active bleeding did not stop after 20 minutes that the standard of care was followed.

Statistical methods

The analytical plan called for bivariate analyses by:

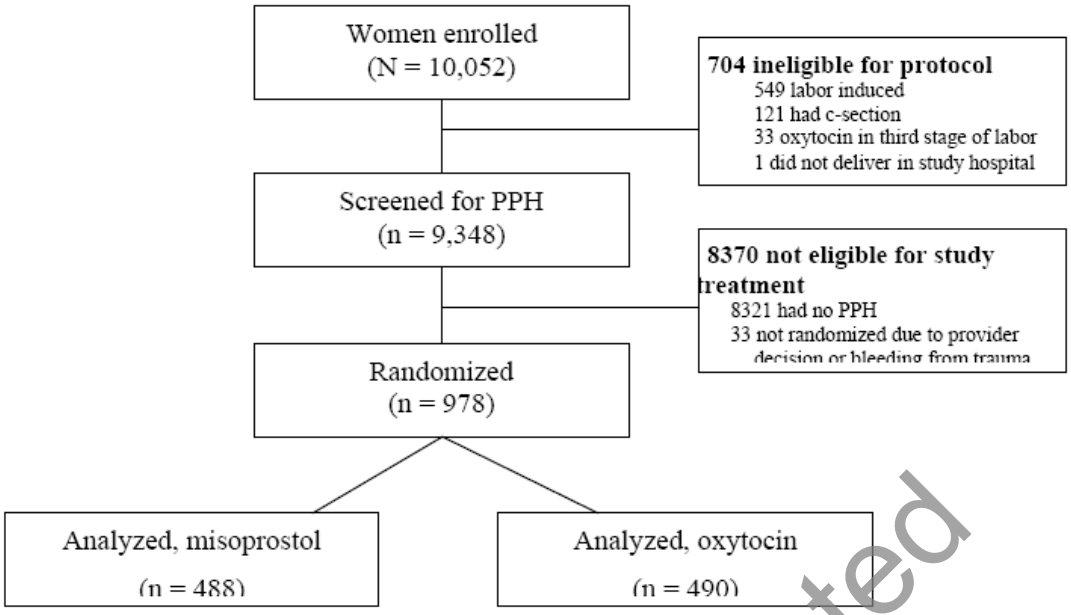
- intention to treat and
- by actual receipt of and compliance with oxytocin or misoprostol intervention.

The analysis plan called for univariate analysis with the independent variable of study arm and dependent variables including additional uterotonics/intervention, additional blood loss >300 mL, mean blood loss, % severely anaemic postpartum, mean change in haemoglobin levels, adverse events, frequency of side effects, and acceptability. Planned multivariate analyses included the same independent and dependent variables with controlling for socioeconomic and reproductive health covariates.

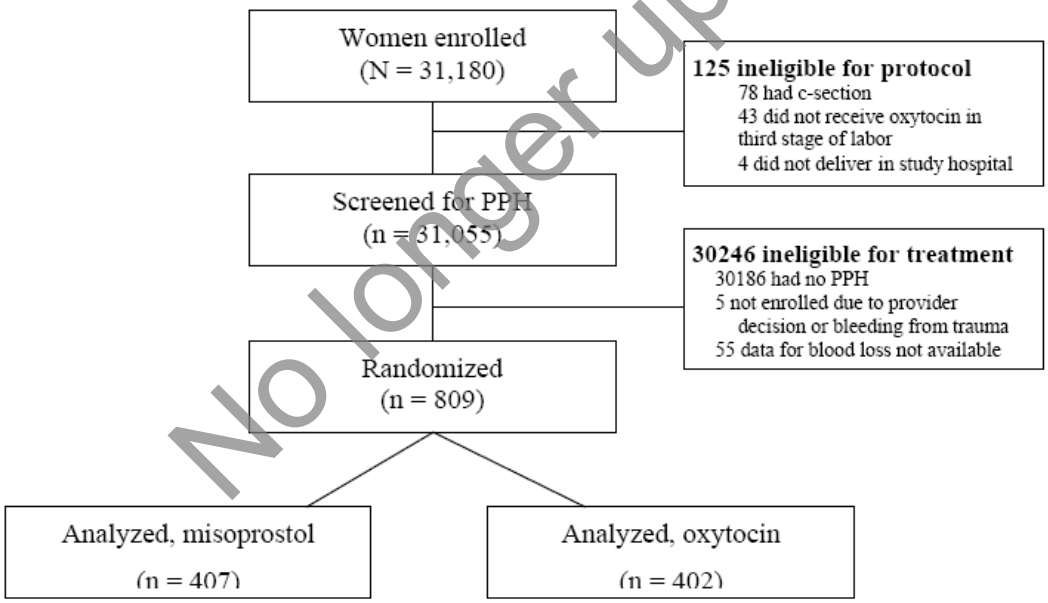
The actual analysis included risk difference and 97.5% CI with a one-sided probability for the primary outcome (cessation of active bleeding within 20 minutes of initial study treatment). Stratified analyses by site were undertaken to explore statistical heterogeneity of effect between sites. Comparisons between treatment groups were done and tested for statistical significance with ×2 tests and Fisher exact tests for categorical variables and t tests and Mann-Whitney U tests for continuous variables. Relative risk and 95% confidence intervals were calculated as appropriate.

Results

Participant flow HMP061202



Participant flow HNP061201:



Recruitment

Study HMP061202:

Studied period: 2005-2008 (first enrolment: 15 August 2005; (last patient completed): 14 Dec. 2007.

Of the 10,052 women enrolled, 704 were excluded for the following reasons: 549 had their labour induced; 121 had a c-section; 33 received oxytocin during the third stage of labour; 1 did not deliver at the study hospital.

Of the 9348 women screened for PPH, 8370 were not eligible for treatment for the following reasons: 8321 did not have PPH; 33 were not randomized because of the provider's decision or because bleeding was considered to be due to trauma; 16 did not have data available for blood loss.

Study HMP061201:

Studied period: 2005- 2008 (first enrolment): 08 Aug. 2005; (last completed): 24 Jan. 2008

Of the 31,180 women enrolled, 78 were excluded due to c-section, 43 did not receive oxytocin during the third stage of labour, 4 did not deliver at the study hospital, 30,186 did not experience PPH, 5 were not enrolled because of the provider's decision or because bleeding was considered to be due to trauma, and 55 did not have data available for blood loss.

Conduct of the studies

There were no Protocol amendments in Study HMP061202, nor Study HMP061201.

A local study coordinator was responsible for ensuring data collection, data entry and adherence to protocol. The sponsor of the study was responsible for study design, protocol development, provision of all study supplies and drugs, monitoring and analysis of study results. Monitoring continued throughout the trial to ensure protocol adherence, and an independent Data Safety and Monitoring Board (DSMB) undertook one interim review when two-thirds of enrolment was available for analysis, and one final review when enrolment was complete (study HMP061202).

The trial HMP061201 was closed when 809 women had been enrolled. The decision to end the study early was made with advice from the DSMB and expert advisers, after interim analysis showed that none of the primary outcomes had reached significance and showed near-zero probability of reaching even marginal significance. It was therefore determined that non-inferiority had been shown and that the logistical considerations and financial costs of continuing, as well as the public health importance of the results, warranted immediate dissemination of these findings.

Baseline data

The study populations consisted of 978 women in study HMP061202 and 809 in study HMP061201, demographic and other baseline characteristics in the study arms are presented in the tables (extracted from the Lancet papers).

Study HMP061202

Table 6

	Misoprostol (n=488)	Oxytocin (n=490)
Age (years)		
Mean (SD)	25 (6)	25 (5)
Range	14–42	15–45
Currently married	464 (95%)	462 (94%)
Educational attainment*		
No education	68 (14%)	48 (10%)
Primary	142 (29%)	148 (30%)
Secondary and higher	278 (57%)	293 (60%)
Number of livebirths†		
0	222 (46%)	227 (46%)
1–3	247 (51%)	250 (51%)
≥4	18 (4%)	13 (3%)
Duration of gestation at delivery (weeks)		
Mean (SD)	39·3 (1·2)	39·2 (1·3)
Range	33·5–43·1	32·0–43·0
Known previous PPH	9 (2%)	19 (4%)
Haemoglobin before delivery (g/L)		
Mean (SD)	121 (16)	120 (17)
Range	82–169	79–163
Suturing after delivery	360 (74%)	366 (75%)
Labour induction or augmentation	0	0
Oxytocin prophylaxis	0	0
Early cord clamping	362 (74%)	367 (75%)
Controlled cord traction	316 (65%)	298 (61%)
Uterine massage	277 (57%)	264 (54%)
Mean time to placental delivery (min [SD])‡	9·4 (9·1)	9·2 (8·4)
Blood loss at time of PPH treatment (mL)		
Median (IQR)	700 (670–800)	700 (680–800)
Mean (SD)	765 (185)	744 (150)
Range	400–1800	450–1500

Data are number (%), unless otherwise indicated. PPH=post-partum haemorrhage. *Data were not available for one woman in the oxytocin group. †Data were not available for one woman in the misoprostol group. ‡Data were not available for four women in the misoprostol group and for two in the oxytocin group.

Table 1: Women's baseline characteristics

Study HMP061201

Table 7

	Misoprostol (n=407)	Oxytocin (n=402)
Age (years)		
Mean (SD)	25 (5·3)	25 (4·8)
Range	16–46	15–43
Currently married	402 (99%)	397 (99%)
No education	109 (27%)	96 (24%)
Number of livebirths		
0	254 (62%)	263 (65%)
1–4	149 (37%)	136 (34%)
≥5	3 (1%)	2 (<1%)
Duration of gestation at delivery (weeks)		
Mean (SD)	39·4 (1·2)	39·5 (1·2)
Range	33–42	30–43
Known previous PPH	12 (2·9)	9 (2·2)
Haemoglobin before delivery (g/L)		
Mean (SD)	112 (14)	113 (13)
Range	67–159	72–150
Labour induced	0	3 (1%)
Labour augmented	213 (52%)	205 (51%)
Oxytocin prophylaxis given	407 (100%)	402 (100%)
Suturing after delivery	200 (49%)	187 (47%)
Early cord clamping	378 (93%)	378 (94%)
Controlled cord traction	346 (85%)	343 (85%)
Uterine massage	298 (73%)	299 (74%)
Mean time to placental delivery (min [SD])	7·4 (8·3)	6·9 (5·3)
Blood loss at time of PPH treatment (mL)		
Median (IQR)	700 (700–750)	700 (700–750)
Mean (SD)	742 (114)	741 (109)
Range	500–1500	500–1800

Data are number (%), unless otherwise indicated. PPH=post-partum haemorrhage.

Table 1: Women's baseline characteristics

Demographic and other baseline characteristics were similar in both study arms.

Numbers analysed

In both studies, all patients who were allocated to a treatment group (488 in the misoprostol group and 490 in the oxytocin group) were included in the efficacy analysis as in the final data, the receipt and compliance rate was perfect thus the ITT group and actual receipt group were identical. Therefore, only Intent to treat (ITT) analysis was conducted.

Outcomes and estimation

Study HMP061202:

Primary efficacy endpoints:

- The success rate (defined as active bleeding stopped within 20 minutes of initial treatment) in the misoprostol arm was 90% and in the oxytocin arm was 96% (relative risk 0.94, 95% CI 0.91–0.98). crude difference 5.3%, 95% CI 2.6 – 8.6).
- Additional blood loss of at least 300 mL after treatment occurred for 30% of women receiving misoprostol and 17% of women receiving oxytocin (relative risk 1.78, 95% CI 1.40–2.26).

Study HMP061201:

- The success rate (defined as active bleeding controlled within 20 min after initial treatment) in the misoprostol arm was 89% in women given misoprostol and 90% in women given oxytocin (relative risk [RR] 0.99, 95% CI 0.95 – 1.04; crude difference 0.4%, 95% CI 3.9 - 4.6).
- Additional blood loss of 300 mL or greater after treatment occurred for 139 (34%) women receiving misoprostol and 123 (31%) receiving oxytocin (RR 1.12, 95% CI 0.92 – 1.37).

Secondary efficacy endpoints and ancillary analyses

Study HMP061202:

The outcome of other measurements is shown below (the table in the Lancet has been copied):

Table 8

	Misoprostol (n=488)	Oxytocin (n=490)	RR (95% CI)	p value
Primary outcomes				
Active bleeding controlled within 20 min with initial uterotonic treatment	440 (90%)	468 (96%)	0·94 (0·91–0·98)	0·001
Additional blood loss ≥300 mL	147 (30%)	83 (17%)	1·78 (1·40–2·26)	<0·0001
Secondary outcomes				
Time to active bleeding controlled (min)				
Median (IQR)	13 (10–16)	11 (8–15)	..	0·001
Mean (SD)	13·4 (8·2)	11·8 (6·6)	..	0·001
Range	0–84	0–77	..	..
Additional blood loss after treatment given (mL)				
Median (IQR)	200 (110–300)	150 (100–225)	..	<0·0001
Mean (SD)	244 (186)	190 (174)	..	<0·0001
Range	0–1100	0–2250	..	..
Additional blood loss ≥500 mL after treatment	53 (11%)	20 (4%)	2·84 (1·63–5·01)	<0·0001
Additional blood loss ≥1000 mL after treatment	5 (1%)	3 (1%)	1·67 (0·40–6·96)	0·360
Total blood loss when active bleeding stopped (mL)				
Median (IQR)	900 (810–1100)	850 (800–1000)	..	..
Mean (SD)	1009 (297)	935 (244)	..	<0·0001
Range	450–2500	450–3500	..	..
Hb after treatment (g/L)*				
Median (IQR)	98 (88–108)	100 (91–109)	..	0·052
Mean (SD)	98 (14)	101 (14)	..	0·025
Range	58–145	59–144	..	..
Drop in Hb ≥20 g/L or blood transfusion	250 (51%)	230 (47%)	1·09 (0·96–1·24)	0·101
Drop in Hb ≥30 g/L or blood transfusion	199 (41%)	148 (30%)	1·35 (1·14–1·60)	<0·0001
Additional interventions				
Additional uterotonic drugs	61 (13%)	31 (6%)	1·98 (1·31–2·99)	0·001
Blood transfusion	41 (8%)	26 (5%)	1·58 (0·98–2·55)	0·036
Hysterectomy/other surgery	0	0	..	..
Exploration under anaesthesia	99 (20%)	90 (18%)	1·10 (0·85–1·43)	0·249
Fluids and/or plasma expanders	89 (18%)	47 (10%)	1·90 (1·37–2·65)	<0·0001
Bimanual compression	294 (60%)	283 (58%)	1·04 (0·94–1·16)	0·234
Maternal death	0	0	..	..

Data are number (%), unless otherwise indicated. RR=relative risk. Hb=haemoglobin. *Post-partum haemoglobin measure excludes women receiving blood transfusion.

Table 2: Primary and secondary outcomes

HMP061201:

Table 9

	Misoprostol (n=407)	Oxytocin (n=402)	RR (95% CI)	p value
Primary outcomes				
Active bleeding controlled within 20 min with initial uterotonic treatment	363 (89%)	360 (90%)	0·99 (0·95–1·04)	0·867
Additional blood loss ≥300 mL after treatment	139 (34%)	123 (31%)	1·12 (0·92–1·37)	0·146
Secondary outcomes				
Time to active bleeding controlled (min)				
Median (IQR)	20 (15–20)	18 (10–20)	..	..
Mean (SD)	19·3 (15·0)	19·1 (14·6)	..	0·854
Range	0–145	0–122	..	
Additional blood loss after treatment given (mL)				
Median (IQR)	200 (100–350)	200 (100–300)	..	0·199
Mean (SD)	279 (251)	252 (205)	..	..
Range	0–2050	20–1100	..	..
Additional blood loss ≥500 mL after treatment	58 (14%)	53 (13%)	1·09 (0·77–1·54)	0·713
Additional blood loss ≥1000 mL after treatment	11 (3%)	3 (1%)	3·62 (1·02–12·89)	0·062
Total blood loss when active bleeding stopped (mL)				
Median (IQR)	900 (850–1100)	900 (800–1100)	..	0·283
Mean (SD)	1024 (300)	997 (263)	..	..
Range	650–3000	640–2100	..	..
Hb after treatment (g/L)*				
Mean (SD)	96 (13)	97 (14)	..	0·229
Range	54–137	50–136	..	..
Drop in Hb ≥20 g/L or blood transfusion	152 (37%)	142 (35%)	1·06 (0·88–1·27)	0·567
Drop in Hb ≥30 g/L or blood transfusion	104 (26%)	90 (22%)	1·14 (0·89–1·46)	0·301
Additional interventions				
Additional uterotonic drugs	40 (10%)	46 (11%)	0·86 (0·58–1·28)	0·260
Blood transfusion	24 (6%)	18 (4%)	1·32 (0·73–2·39)	0·229
Hysterectomy	4 (1%)	2 (<1%)	1·98 (0·36–10·73)	0·350
Exploration under anaesthesia	37 (9%)	22 (5%)	1·66 (1·00–2·76)	0·032
Bimanual compression	39 (10%)	31 (8%)	1·24 (0·79–0·95)	0·209
Other surgery or any other procedure	6 (1%)	7 (2%)	0·85 (0·29–2·50)	0·982
Maternal death	1 (<1%)	1 (<1%)	0·99 (0·06–15·74)	0·747

Data are number (%), unless otherwise indicated. RR=relative risk. Hb=haemoglobin. *Post-partum haemoglobin measure excludes women receiving blood transfusion.

Table 2: **Primary and secondary outcomes**

Summary of main studies in the treatment of post partum haemorrhage

The following tables summarise the efficacy results from studies HMP061202 and HMP061201. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of efficacy for main trial HMP061202

Title: treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet 2010;375:210-6					
Study identifier	HMP061202				
Design	Double-blind, double-dummy, randomised, active controlled, non-inferiority trial				
	Date of first enrollment: 15 Aug 2005 Date of last completed 14 Dec 2007 Duration of Extension phase: NA				
Hypothesis	Non-inferiority versus oxytocin				
Treatments groups	Women with PPH suspected due to uterine atony who did not receive prophylactic oxytocin: Misoprostol 800 mcg sublingual (4 tablets of 200 mcg) + placebo IV injection, Single dose, 488 women randomized Women with PPH suspected due to uterine atony who did not receive prophylactic oxytocin: Oxytocin 40 IU intravenous + 4 placebo tablets, 490 randomized				
Endpoints and definitions	2 Co-Primary endpoints: 1. cessation of active bleeding within 20 minutes with initial uterotonic treatment 2. additional blood loss of 300 mL or more after treatment				
	Secondary endpoints: - Time to active bleeding controlled (min) - Additional blood loss after treatment (mL) - Additional blood loss ≥ 500 mL - Additional blood loss ≥ 1000 mL - Total blood loss when active bleeding stopped (mL) - Hb after treatment - Drop in Hb ≥ 20 g/L or blood transfusion - Drop in Hb ≥ 30 g/L or blood transfusion				
	Secondary other: - Additional interventions (additional uterotonic drugs, hysterectomy, etc, and death)				
Database lock	Not stated				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability	Treatment group	Misoprostol 800 mcg sublingual	Oxytocin 40 IU iv	RR (95% CI) Risk difference (95% CI)	P-value
	Number of subjects	488	490		
	Active bleeding controlled in 20 minutes (%)	440 (90%)	468 (96%)	**0.94(0.91-0.98) 5.3% (2.6-8.6)**	0.001
	Additional blood loss ≥ 300 mL (%)	147(30%)	83 (17%)	**1.78 (1.40-2.26)** risk difference not available	<0.0001

	Key secondary endpoints:				
	Additional BL ≥ 500 mL	53 (11%)	20 (4%)	1.84 (1.63-5.01)	<0.0001
	Additional BL ≥ 1000 mL	5 (1%)	3 (1%)	1.67 (0.40-6.96)	0.360
	Drop in Hb ≥ 20 g/L or blood transfusion	250 (51%)	230 (47%)	1.09 (0.96-1.24)	0.101
	Drop in Hb ≥ 30 g/L or blood transfusion	199 (41%)	148 (30%)	1.35 (1.14-1.60)	<0.0001

Table 11 Summary of efficacy for trial HMP061201

Title: treatment of postpartum haemorrhage with sublingual misoprostol versus oxytocin in women **receiving prophylactic oxytocin**: a double-blind, randomised, non-inferiority trial Lancet 2010;					
Study identifier	HMP061201				
Design	Double-blind, double-dummy, randomised, active controlled, non-inferiority trial				
	Date of first enrollment: Date of last completed Duration of Extension phase:	8 Aug 2005 24 Jan 2008 not applicable			
Hypothesis	Non-inferiority				
Treatments groups	Women with PPH suspected due to uterine atony who received prophylactic oxytocin	Misoprostol 800 mcg sublingual (4 tablets of 200 mcg), Single dose, 407 women randomized + placebo IV injection			
	Women with PPH suspected due to uterine atony who received prophylactic oxytocin	Oxytocin 40 IU intravenous + 4 placebo tablets, 402 randomized			
Endpoints and definitions	2 Co-Primary endpoints	1. cessation of active bleeding within 20 minutes 2. additional blood loss of 300 mL or more after treatment			
	Secondary endpoints	Time to active bleeding controlled (min) Additional blood loss after treatment (mL) Additional blood loss ≥ 500 mL Additional blood loss ≥ 1000 mL Total blood loss when active bleeding stopped (mL) Hb after treatment Drop in Hb ≥ 20 g/L or blood transfusion Drop in Hb ≥ 30 g/L or blood transfusion			
	Secondary other:	Additional interventions (additional uterotonic drugs, hysterectomy, etc, and death)			
Database lock	Not stated				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (no protocol violations)				
Descriptive statistics and estimate variability	Treatment group	Misoprostol 800 mcg sublingual	Oxytocin 40 IU iv	RR (95% CI) Risk difference (95% CI)	P-value
	Number of subject	407	402		

	Primary endpoints: **Active bleeding controlled in 20 minutes (%)**	363 (89%)	360 (90%)	**0.99 (0.95-1.04) 0.4% (-3.9 – 4.6)**	0.867
	Co-primary endpoint: **Additional blood loss ≥ 300 mL (%)**	139 (34%)	123 (31%)	**1.12 (0.92-1.37)** Risk difference not available	0.146
	Key secondary endpoints:				
	Additional blood loss ≥ 500 mL	58 (14%)	53 (13%)	1.09 (0.77-1.54)	0.713
	Additional blood loss ≥ 1000 mL	11 (3%)	3 (1%)	3.62 (1.02-12.89)	0.062
	Drop in Hb ≥ 20 g/L or blood transfusion	152 (37%)	142 (35%)	1.06 (0.88-1.27)	0.567
	Drop in Hb ≥ 30 g/L or blood transfusion	104 (26%)	90 (22%)	1.14 (0.89-1.46)	0.301

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

2.5.3. Discussion on clinical efficacy in the treatment of PPH

Design and conduct of clinical studies

Both treatment studies had a double-blind, double-dummy active controlled design to test non-inferiority versus oxytocin, which is considered an adequate design to evaluate relative efficacy and safety in the indication requested. The reference product is considered an adequate choice.

However, in the context of this application and with regards to treatment of post-partum haemorrhage and prophylactic treatment with oxytocin in one of the studies (trial HMP061201), it should be noted that the use of oxytocin during the third stage of labour may not be standard treatment in the areas where the applicant is aiming to market misoprostol. Furthermore, this design of pre-use of oxytocin could have rendered the study insensitive to detect differences between misoprostol and oxytocin. The study (HMP061201) is considered supportive only.

Dose selection and route of administration:

Single dose of 800 mcg misoprostol sublingually administered.

The selected dose and route of administration of misoprostol in the indication requested were not based on dose-response studies. From past experience there was no consensus on the optimal misoprostol dose and route of administration for PPH treatment. For the treatment studies submitted, a dose high enough to demonstrate efficacy when compared with IV oxytocin

(800mcg) was selected based on published literature, expert opinion and pharmacokinetic information. This dose had previously been tested in an RCT on misoprostol use for first–line PPH treatment and did not result in excessive side effects (Lokugamage 2001 (313); the results of the study suggested that an 800 – 1,000 mcg rectal dose of misoprostol may be as effective as syntometrine for PPH treatment. According to the study conductors, pharmacokinetic studies have shown that the sublingual route is associated with rapid absorption, high serum peak levels, and the highest bioavailability compared with all other routes tested, making it a promising route for treatment of PPH. In conclusion, there is no dose response study. More information about the tolerability was collected in an uncontrolled pilot study performed in Quito (the treatment site that reported highest frequency of fever) after completion of the two published treatment trials submitted in support of this indication; 600 mcg misoprostol was used in this study. Although side effects occurred more frequent with the 800 mcg, there was no suggestion that the degree of severity of side effects with the 800 mcg dose were relevantly higher than with the 600 mcg. Further information is discussed in the safety section. As to the indirect comparison of efficacy, although no definite conclusions can be drawn, the results suggest higher efficacy with the 800 mcg dose.

In terms of the convenience of sublingual administration of 4 tablets which have to be melted under the tongue for 20 minutes, see clinical discussion in section 2.5.8.

The active comparator Oxytocine dose was 40 IU by intravenous infusion over 15 minutes, i.e. a rather high dose. The sponsor extensively consulted the literature on PPH and uterotonics and convened an expert advisory group to discuss the selection of the dose. There are several recommended doses of oxytocin for PPH treatment. The RCOG guidelines (2009) recommend 40 IU of oxytocin via 500 mL slow infusion, the WHO recommended 20 IU in 1 liter at 60 drops per minute and the SPC for Syntocinon recommends 5 IU followed by 5 – 20 IU by infusion. There was also disagreement among experts over which dose was “standard” and in fact, many of the experts the sponsor consulted expressed that they use a range of doses. In view of these different approaches and in the absence of RCTs showing the efficacy of any of these regimens, the investigators elected to use the maximum dose of oxytocin (so 40 IU as opposed to 20 IU as commonly used) to ensure the strictest level of comparison between the two uterotonics. This is considered acceptable.

In study HMP061201, the women routinely received oxytocin 5IU/10IU given either intravenously or intramuscularly within one minute of delivery as prophylaxis in the 3rd stage of labour as part of active management of the third stage of labour (AMSL). This dose was based on WHO recommendations at that time.

Inclusion- and exclusion criteria:

Inclusion and exclusion criteria are considered adequate for the indication requested and in line with the study design.

Cut off level of 700 mL is considered adequate in the indication of treatment of PPH. It is acknowledged that the definition of the WHO, which defines PPH as bleeding from the genital tract of 500 mL or more within the first 24 hours of birth of the baby (WHO 2000) has been criticised (Bloomfield 1990)on the basis of the clinical relevance of the cut-off for postpartum blood loss of 500 mL in women with normal haemoglobin (Hb) levels before birth.

Blinding:

The rationale that double-blind, double dummy approach will succeed, i.e. the treating physicians and patients will not be able to discern the treatment they receive, as the mode of action and type of adverse events resemble is not fully endorsed. Misoprostol has fever as a specific adverse event, while this is not the case with oxytocin. However, this approach can be considered adequate for the proposed indication.

Primary efficacy endpoints selected:

The Co-primary endpoints ***of percentage cessation of active bleeding within 20 minutes of treatment and percentage of additional blood loss of 300 mL or more after treatment*** are considered suitable for efficacy evaluation in the indication requested.

Statistical methods:

The statistical analysis plan consists of descriptions in the trials' protocols and dummy tables. These were finalised and all data was collected prior to unblinding of the treatment codes.

The actual analysis included risk difference and 97.5% CI with a one-sided probability for the primary outcome (cessation of active bleeding within 20 minutes of initial study treatment). According to the company if additional measures were used to stop bleeding in any subjects, they were considered failures and analysed as such. In order to show non-inferiority, a ***non-inferiority margin of 6%*** was defined. This difference of 6% was based on a literature review and discussion with experts in the field and was chosen "as the smallest value that would be a clinically important effect".

The ITT and PP populations were defined post hoc. The ITT population included all consenting women randomised to receive PPH treatment. The PP population included all women who received the study medication and for whom follow up data was collected. The ITT and PP population were identical. Missing data was handled by excluding patients from analysis. There was no missing data on the primary and secondary endpoints, only on socio/demographic variables. A justification of this handling of missing data is lacking, no sensitivity analyses were performed to account for missing data.

No adjustment for multiplicity was defined a priori, the primary endpoints were analysed as co-primary endpoints, therefore both had to be statistically significant. The applicant performed multiplicity adjustment for the primary endpoints post-hoc and the results did not change the conclusions. No multiplicity adjustment was performed for the secondary endpoints.

Overall, there were significant concerns regarding the statistical methodology of the studies (HP061201 and HP061202) but it is acknowledged and noted that they were not performed by the applicant but by an independent organisation; the applicant only supplied the tablets. Therefore, these studies (HP061201 and HP061202) conducted in support of the treatment of post-partum haemorrhage were not conducted according to regulatory requirements and pursuing these statistical issues is not expected to lead to more information. Despite these shortcomings, the CHMP was of the opinion that the effect size in the misoprostol arm of study HMP061202 was such that efficacy can be inferred; study HMP061201 is considered as supportive only.

Sample size:

The studies were designed as non-inferiority trials. Oxytocin was postulated to stop bleeding within 20 minutes for ***88% of women***. No trials had been previously published on the efficacy of oxytocin; therefore its efficacy as the reference treatment was based on expert opinion. It was assumed that misoprostol would work similarly and that a ***6% margin of inferiority*** would be acceptable as clinically equivalent in public health terms. Based on these assumptions, for 80% power, α of .05, and a one-sided test, + additional 10% planned to account for protocol violations or loss to follow up 479 per study group was calculated. Thus, the sample size is not based on clinical data, but directed by expert opinions and a literature review.

Study populations:

The study without prophylactic oxytocin was performed in hospitals in Ecuador, Egypt, and Vietnam, while the study in which women were prophylactically treated with oxytocin was performed in Burkina Faso, Turkey, Egypt, and Vietnam.

Efficacy data and additional analyses

Study **HMP061202 in *women who have not received oxytocin prophylactically*** during the third stage of labour:

Outcome primary efficacy endpoints:

- The success rate (defined as active bleeding stopped within 20 minutes of initial treatment) in the misoprostol arm was 90% and in the oxytocin arm 96% (relative risk 0.94, 95% CI 0.91–0.98). The crude difference is 5.3% (95% CI 2.6 – 8.6).
- Additional blood loss of at least 300 mL after treatment occurred for 30% of women receiving misoprostol and 17% of women receiving oxytocin (relative risk 1.78, 95% CI 1.40–2.26). The crude difference was not presented.

Based on these results, the objective of the study, i.e. showing non-inferiority to oxytocin was not achieved in study HMP061202 in which women did not receive oxytocin prophylactically in the third stage of labour; the success rate noted for misoprostol is outside the predefined non-inferiority margin and the percentage of additional blood loss of at least 300 mL was notably higher.

Study **HMP061201 in *women who have received oxytocin prophylactically*** during the third stage of labour:

- The success rate (defined as active bleeding controlled within 20 min after initial treatment) in the misoprostol arm was 89% in women given misoprostol and 90% in women given oxytocin (relative risk [RR] 0.99, 95% CI 0.95 – 1.04; the crude difference is 0.4%, 95% CI 3.9 - 4.6).
- Additional blood loss of 300 mL or greater after treatment occurred for 139 (34%) women receiving misoprostol and 123 (31%) receiving oxytocin (RR 1.12, 95% CI 0.92 – 1.37). The crude difference was not presented.

The results of this second study HMP061201 suggest that misoprostol is non-inferior to oxytocin with regard to the first primary endpoint. For the second primary endpoint, the relative risk and

its 95% CI also suggest there is no difference between misoprostol and oxytocin. In addition, the applicant provided an analysis comparing the total blood loss of all patients screened for studies HMP061201 and HMP061202. The histograms of blood loss showed two peaks. Most women had a blood loss of 200-300ml, but there was also a peak in the histograms around 900 ml. According to the Applicant, this second peak represented women who stopped bleeding shortly after PPH treatment, and the percentage of women responding to treatment was calculated in this way. Although this second peak may represent treatment responders, it is unclear how this data was analysed and whether these response percentages were statistically significant. Nevertheless, it does suggest that treatment with Hemoprostol provides a benefit similar to oxytocin.

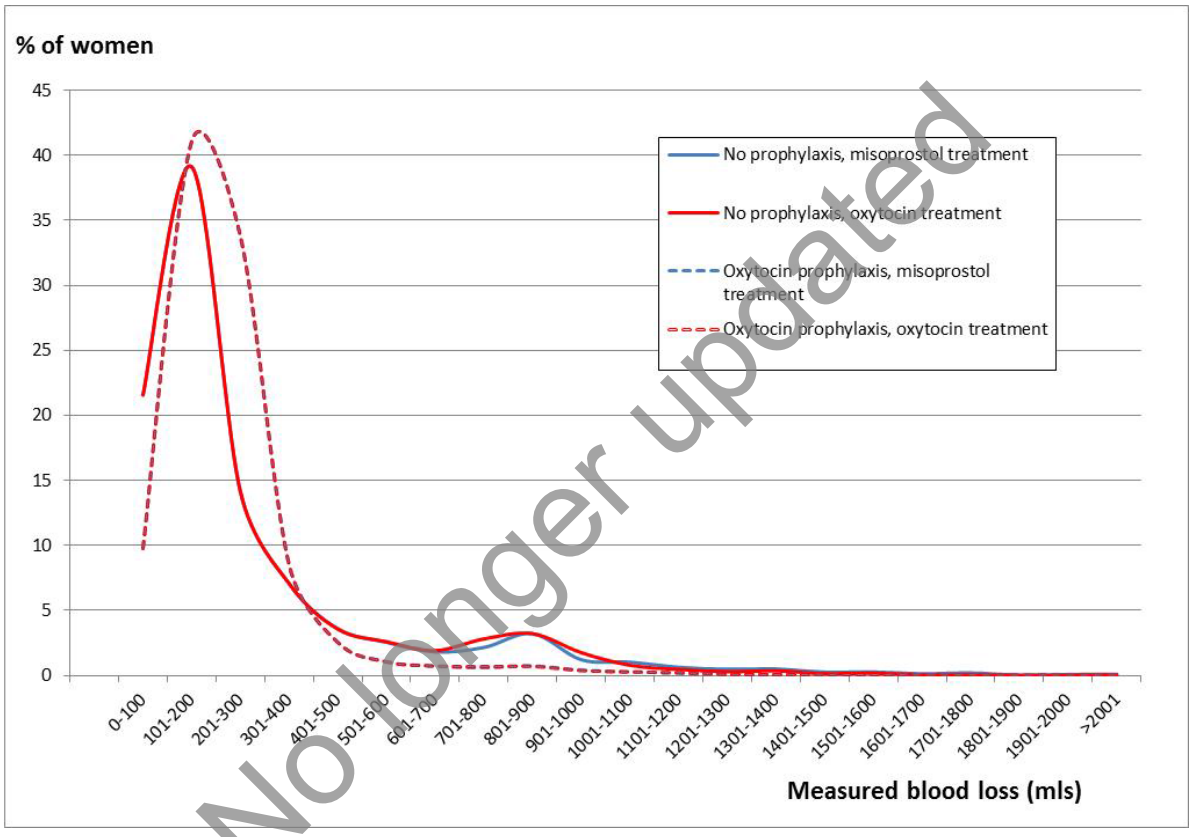


Figure 4. Blood loss histograms (smoothed) for women enrolled into the randomised trials by Winikoff (2010) and Blum (2010).

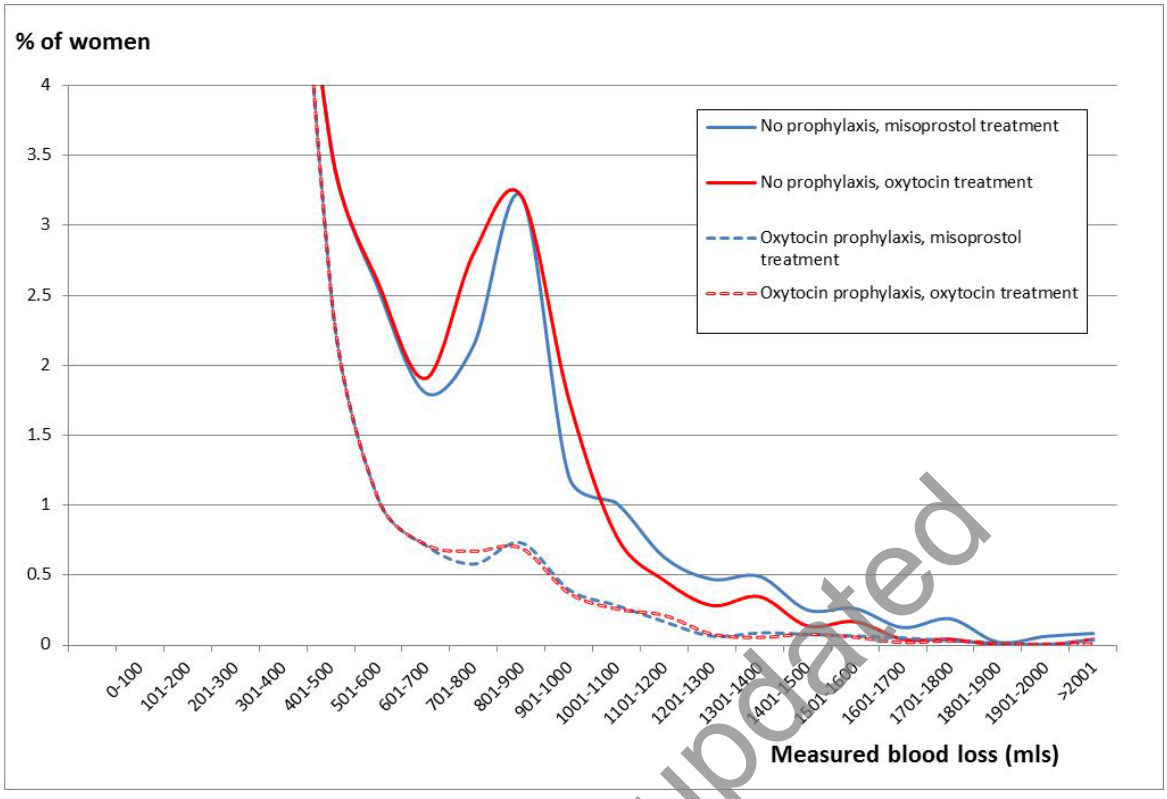


Figure 5: An expanded graph showing the same data as for Figure 4, but with an expanded y-axis to show the detail.

Key secondary endpoints

The secondary endpoints that are considered the most relevant for this application are:

- Blood loss after treatment, total, ≥500 mL, and ≥1000 mL
- Drop in Hb ≥20 g/L; ≥30 g/L and total change in Hb after treatment, followed the outcome of the primary efficacy endpoints, i.e. in study HMP061202, outcomes in the oxytocin group were favourable in comparison to the misoprostol group, while in study HMP061201, no clear differences between groups were noted.

2.5.4. Conclusions on clinical efficacy in the treatment of PPH

The data results of the published study **HMP061202**, in which no prophylactic oxytocin was given in the 3rd stage of labour, showed efficacy of misoprostol in the treatment of PPH, i.e. 90% versus 96% in the oxytocin arm of women in whom active bleeding had stopped within 20 minutes of initial treatment. Although non-inferiority versus oxytocin could not be established, the effect size in the misoprostol arm is such that efficacy can be concluded. It is considered that 90% is incontrovertibly a positive effect which if this was an uncontrolled trial will be acceptable especially within the context of post-partum haemorrhage where the effects can lead to severe morbidity and mortality.

In the other study **HMP061201**, that selected women who were given prophylactic oxytocin in the 3rd stage of labour, non-inferiority versus oxytocin was achieved on one of the two primary endpoints (89% versus 90% of women in whom cessation of active bleeding had stopped within 20 minutes), again demonstrating clinically meaningful efficacy. However, the population selected in this study is not comparable with the population aimed for, as the intended population would not have access to oxytocin. Additionally, the prophylactic use of oxytocin could have rendered the study insensitive to detect differences between misoprostol and oxytocin. Therefore, this study is considered as supportive only.

Overall, even though the statistical documentation is not considered optimal, data are considered to be adequate in order to draw conclusions on the results. In terms of the request to present data in support of efficacy of treatment versus no treatment, the Applicant indicated that no such data exist, due to ethical concerns regarding no treatment in a context where misoprostol would be the only option for those diagnosed with post-partum haemorrhage and requiring care. However, in the absence of such direct clinical data it could also have been beneficial to estimate risk of PPH in remote areas if no treatment would be available; in other words what would be the consequence with regard to the safety of women when there is no PPH treatment available at all.

Of maternal deaths, haemorrhage is still the leading cause of death in Africa (point estimate 33·9%, range 13·3–43·6; eight datasets, 4508 deaths) and in Asia (30·8%, 5·9–48·5; 11, 16089)[6], these figures indicate that the risk of dying from post-partum haemorrhage is about 100 times higher in developing countries than in developed countries. Bearing in mind that PPH can be effectively treated, one of the reasons for this discrepancy is thought to be due to restricted access to uterotonics, higher likelihood of deliveries being inadequately supervised, and geographic isolation. Although oxytocin remains the drug of choice to treat excessive post-partum bleeding, access to it can be difficult in resource-poor settings, because of its requirements for storage, skilled personnel, and parenteral administration.[7],[8]

Taking the above into account and also the fact that in the absence of medical treatment the morbidity and mortality of PPH can be considerable, it is considered that not using misoprostol will be associated with a worse outcome than seen in the two clinical studies submitted. The results of these studies showing that misoprostol is effective to a great extent in treating post-partum haemorrhage coupled with the fact that there are several papers available which have demonstrated the efficacy of misoprostol in the treatment of PPH[9],[10],[11],[12,13] including the

[6] *Khalid S, Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367: 1066–74.*
[7] *Ramanathan G, Arulkumaran S. Postpartum hemorrhage.J Obstet Gynaecol Can 2006; 28: 967–73.*
[8] *AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003; 67: 1–11.*
[9] Lokugamage AU, Sullivan KR, Niculescu I, et al. A randomized study comparing rectally administeredmisoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum haemorrhage. Acta Obstet Gynecol Scand 2001; 80: 835–839.
[10] Hofmeyr GJ, Ferreira S, Nikodem VC, et al. Misoprostol for treating postpartum hemorrhage: a randomized controlled trial. BJOG 2004; 111: 1014–19.
[11] Mousa HA, Alfi revic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2007; 1: CD003249.
[12] Hofmeyr GJ, Walraven G, Gülmezoglu AM, Alfi revis Z, Villar J. Misoprostol to treat postpartum hemorrhage: a systematic review. BJOG 2005; 112: 547–53.
[13] Abdel-aleem H, El-Nashar I, Abdel-Aleem A. Management of severe postpartum hemorrhage with misoprostol. Int J Gynaecol Obstet 2001; 72: 75–76.

placebo-controlled RCT by G Walraven et al[14] of which the results suggested that additional blood loss greater than 500ml was lower in the misoprostol group when compared to placebo (16.5 versus 28.4%). In conclusion, although the company has not provided any direct comparison with no treatment, the evidence available indicates that misoprostol is effective in the management of post-partum haemorrhage to a clinically meaningful extent, although less so when compared to oxytocin. Therefore, it can be concluded that misoprostol would be beneficial for the treatment of PPH in situations where oxytocin is not available for various reasons.

In both treatment studies, misoprostol was administered in a hospital setting (secondary-level and tertiary-level facilities). Therefore, it is unclear if the results of these studies can be extrapolated to places outside of hospitals. Subsequently, while the applicant considered that misoprostol should not be subject to medical prescription, the benefit-risk balance of the non-prescription status cannot be assessed. The applicant was requested to discuss in which way current clinical data would justify a positive benefit-risk balance in case the product in the requested indication of treatment of PPH would be granted a non-prescription status (upon recommendation by national regulatory authority), and the proposed benefits of an advanced purchase of misoprostol. However, the applicant has withdrawn the proposal to include prevention of post-partum haemorrhage in the indication and considers therefore that advanced purchase is less of a concern. In treatment of PPH, it is likely that medical staff, midwives or birth attendants duly authorized to assist in delivery depending on national regulations will be the only people allowed to deliver the product for the treatment of post-partum haemorrhage. Advanced purchase of misoprostol would not be justified for treatment of PPH. In every instance, it is anticipated that dispensation of the product will be regulated at national level because not only medical staff, but also midwives or birth attendants are mentioned as potential administrators of Hemoprostol. Therefore, the dispensation and training of this non-medical group of suppliers of the product should be adequately regulated, taking into account the safety concerns discussed in the RMP (see section 2.8); the appropriate tools are to be agreed with the national regulatory authorities.

2.5.5. Dose response studies in the prevention of post partum haemorrhage

No formal dose response studies were performed, but preliminary research was done to evaluate safety profile of two doses selected, see section 'dose selection' below. The dose was selected based on a pilot trial and degree of side effects observed was found acceptable for the 600mcg dose.

[14] Gijs Walraven, Yusupha Dampha, Bubacarr Bittaye, Maimuna Sowe Justus Hofmeyer. Misoprostol in the treatment of postpartum haemorrhage in addition to routine mamagement: aplacebo randomised controlled trial

2.5.6. Main clinical study in the prevention of post partum haemorrhage

Summary of main efficacy results

HMP 061203

The following table summarises the efficacy results from study HMP061203. This summary should be read in conjunction with the discussion and conclusion on clinical efficacy.

Table 12. Summary of efficacy for main trial HMP061203

Title: Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomized placebo-controlled trial. Mobeen et al. BJOG 2011, 118(3):353-61.			
Study identifier	HMP061203		
Design	Double-blind, randomised, placebo-controlled, superiority trial		
	Date of first enrollment: Date of last completed Duration of Extension phase:		not applicable
Hypothesis	Superiority versus placebo		
Treatments groups	-Pregnant women in general good health, residing in one of the 46 study villages, -planning to deliver at home with a study TBA		Misoprostol 600 mcg or (3 tablets of 200 mcg), Single dose, women randomized
	-Pregnant women in general good health, residing in one of the 46 study villages, -planning to deliver at home with a study TBA		3 placebo tablets, single dose, randomized
Endpoints and definitions	2 Co-Primary endpoints	**Blood loss ≥ 500 mL** **Drop in Hb > 2 g/dl**	
	Secondary endpoints	Blood loss ⩾750 ml Blood loss ⩾1000 ml Total blood loss (ml) Haemoglobin Post-delivery Hb Post-delivery Hb < 9 g/dl; Hb < 11 g/dl Change in Hb Drop in Hb > 3 g/dl	
Database lock	Not stated		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (no protocol violations)		

Descriptive statistics and estimate variability	Treatment group	Misoprostol 600 mcg oral	Placebo	RR (95% CI)	P-value
	Number of subject	533	583		
	Primary endpoint: **Blood loss ≥ 500 mL**	85/514 (16.5%)	122/558 (21.9%)	0.76 (0.59-0.97)	-
	Co-primary endpoint: **Drop in Hb > 2 g/dl**	88/528 (16.7%)	120/572 (21.0%)	0.79 (0.62-1.02)	-
	Key secondary endpoints:				
	-Blood loss ≥ 750 mL	29/514 (5.6)	40/558 (7.2)	0.79 (0.50-1.25)	-
	-Blood loss ≥ 1000 mL	10/514 (1.9)	19/558 (3.4)	0.57 (0.27-1.22)	-
	-Post delivery Hb< 9g/dl	27/533 (5.1)	37/581 (6.4)	0.80 (0.49-1.29)	-
	-Post delvery Hb< 11g/dl	182/533 (34.1)	189/581 (32.5)	1.05 (0.89-1.24)	-
	-Drop in Hb > 3g/dl	27/528 (5.1)	55/572 (9.6)	0.53 (0.34-0.83)	-

2.5.7. Discussion on clinical efficacy in the prevention of PPH

Design and conduct of clinical studies

The study had a double-blind, placebo-controlled design to test superiority versus placebo in home births. In this setting, the selection of placebo as the reference is considered an adequate choice, as oxytocin administration needs doctors and facilities for IV administration.

Dose selection and route of administration:

Single dose of 600 mcg misoprostol orally administered. Prior to initiating the WHO trial, a preparatory phase of research was performed to determine which dose of misoprostol to use in the main study, given some concerns about side effects (Lumbiganon 1999). A pilot trial before implementing the main trial was conducted to determine rates of shivering and pyrexia (temperature > 38°C) within one hour after delivery. Oral misoprostol 600 mcg and 400 mcg were compared with 10 IU of oxytocin during the active management of the third stage of labour. The results indicated that shivering was more prevalent in the misoprostol 600 mcg group, but there were no signals that degree of severity with the 600 mcg dose was relevantly higher than with the 400 mcg and should be avoided.

In- and exclusion criteria:

In- and exclusion criteria are considered adequate for the indication requested and in line with the study design.

Blinding:

Whether a double-blind approach will succeed, i.e. the treating TBA's (traditional birth attendants) and patients will not be able to discern the treatment they receive, was not discussed. However, in view of the specific adverse events on body temperature, it is questioned whether the TBA's and patients will remain blind to the treatment given. However, this approach

is considered acceptable regarding the goal of this study, i.e. assessment of efficacy and safety in a home birth situation.

Primary efficacy endpoints selected:

The efficacy endpoints include "postpartum haemorrhage (blood loss ≥ 500 ml)" and "drop in HB of >2 g/dl from pre- to post-delivery".

As to the primary efficacy endpoints, the selection of ≥500 mL might be considered disputable. In clinical practice, many women lose 500 mL in a normal delivery. Additionally, the cut-off of 500 mL has also been criticised on the basis of the clinical relevance of postpartum blood loss of 500 mL in women with normal haemoglobin (Hb) levels before birth (Bloomfield 1990). It was discussed that 500ml within 24 hours of birth may not be a good biological marker but it is the norm of international agencies, treatment guidelines, and training of health workers in less developed countries. This definition is referred to in recent guidelines on the prevention and management of PPH issued by WHO (2012) (390) as well as by RCOG (2009) (367). In study HMP061203, the primary outcome of blood loss ≥500 mL is therefore considered in line with the standard definition of PPH.

The secondary variables selected, including blood loss ≥750 mL and ≥1000 mL, are considered supportive in evaluating the efficacy of misoprostol in the requested indication.

Statistical methods:

The statistical analysis plan consists of descriptions in the trials' protocols and dummy tables. These were finalised and all data was collected prior to unblinding of the treatment codes.

The ITT and PP populations were defined post hoc. The ITT population included all consenting women randomised to receive PPH treatment. The PP population included all women who received the study medication and for whom follow up data was collected. The ITT population excluded patients with missing data on the primary endpoints. This is not appropriate as the reason for the missing data could be related to the treatment. A justification of this handling of missing data is missing; no sensitivity analyses were performed to account for missing data.

No adjustment for multiplicity was defined a priori, the primary endpoints were analysed as co-primary endpoints, therefore both had to be statistically significant. The applicant performed multiplicity adjustment for the primary endpoints post-hoc and the results did not change the conclusions. No multiplicity adjustment was performed for the secondary endpoints.

Furthermore, it is acknowledged that this study was not performed by the applicant but by an independent organisation; the applicant had only supplied the tablets. Therefore, these studies were not conducted in all aspects according to regulatory requirements. Pursuing statistical issues will not lead to more information on this point, as more information is not available.

Sample size:

The study was designed as a superiority trial. A meaningful difference in PPH is assumed as a 35% difference versus placebo, although not stated as such in the study objectives nor in the sample size calculation. In the sample size calculation it was also taken into account that this study also measured the effect of the intervention on change in Hb levels between pre and post delivery and anaemia (<9 g/dL and <11 g/dL). The proportion of women who have a clinically

significant drop in Hb from pre- to post-delivery (>2 g/dL) had been estimated to be 20%, but this was not substantiated by clinical data. The use of a one-sided test, with an α of .05 is not in line with the Guideline on the choice of the non-inferiority margin.

However, the study failed to reach the calculated sample size.

Study populations:

The study was conducted in remote, mountainous villages of Chitral, Khyber Pakhtunkhwa Province, Pakistan where approximately half of all deliveries are conducted by an unskilled traditional birth attendant (TBA) at home. The study locations can be considered representative for the requested application, i.e. relates to the use of misoprostol for the prevention of PPH in countries where intravenous oxytocin cannot be used for any reason.

Efficacy data and additional analyses

Outcome primary efficacy endpoints:

- A significant difference in percentage of PPH ≥500 mL was observed among women receiving 600 µg oral misoprostol, i.e. 16.5% compared to 21.9% of women receiving placebo, resulting in a 24% reduction in PPH.; RR is 0.76 (95% CI 0.59-0.97). A non-significant difference in drop in Hb >2 g/dL was observed among 16.7% of women receiving misoprostol compared to 21.0% of women receiving placebo; RR 0.79 (0.62-1.02).

However, the primary objective of the study, i.e. a meaningful reduction in PPH versus placebo was not defined. In the sample size calculation a difference of 35% versus placebo was assumed, which was not reached in this study based on ITT and per protocol analysis.

Further, analysis of outcomes by year 1 and 2, conducted to explore whether improved delivery practices and study implementation influenced study outcomes, showed a large effect:

- In the first year of the study, the effect of misoprostol on PPH rates and changes in Hb was negligible,
- In the second year, misoprostol was associated with a significant reduction in the rates of PPH (PPH ≥500 mL: RR = 0.69, 95% CI: 0.49–0.99; severe PPH ≥1000 mL: RR = 0.18, 95% CI: 0.04–0.82) and in the proportion of women who experienced a Hb drop >3 g/dL, compared with placebo (RR = 0.38, 95% CI: 0.18–0.80).
- Analysis of the temporal trends within each study arm:
  - No statistically significant reductions in rates of PPH or in Hb changes in the placebo group.
  - In the misoprostol group, 3.3% of women had severe PPH in the first year, compared with 0.7% in the second year (RR = 0.26, 95% CI: 0.06–1.21).
  - Similar trends were observed for drops in Hb >2 and >3 g/dL in the misoprostol group (RR = 0.68, 95% CI: 0.46–1.00; RR = 0.47, 95% CI: 0.21–1.02, respectively).

These temporal trends underscored the importance of continual support, training, and skill-building. In the second year of the study, misoprostol was associated with significant reduction in

postpartum bleeding and in the proportion of women who experienced clinically important changes in haemoglobin concentrations; whereas the first year did not produce any measurable differences between the two study arms. These trends suggest that other factors besides uterotonic potency, such as improved implementation, training and delivery skills, may have contributed to misoprostol's measurable effect on PPH prevention in the second year of the study.

Outcome key secondary endpoints:

- Blood loss ≥750 ml and ≥1000 ml
- Total blood loss (ml)
- Post-delivery Hb < 9 g/dl; Hb < 11 g/dl, Change in Hb pre- and post delivery
- Drop in Hb > 3 g/dl

These followed the outcome of the primary efficacy endpoints, no clear differences between groups were noted, except for a drop in Hb >3 g/L.

2.5.8. Conclusions on clinical efficacy in the prevention of PPH

In terms of the clinical data provided, the results of the single published study provided in support of this indication clearly show that there were difficulties with its conduct. Although regular monitoring and training of study staff and traditional birth attendants (TBAs) were continued throughout the duration of the trial, the first 7 months of the study were deleted from the study results, as the collected data were invalid.

Based on the study results, the objective of the study, i.e. showing superiority to placebo was not achieved. Additionally, it appeared that efficacy is related to the educational level of the TBA. When the remaining results collected during June 2006-2007 and June 2007-June 2008 were divided into a first and second treatment year, it was shown that only in the second year the prevention arm showed some favourable effects over placebo. The question is therefore whether the results present the efficacy of misoprostol alone or misoprostol in combination with a training program of the unskilled TBA.

As to the request to present a robust discussion of the benefit of misoprostol prevention versus no prevention, the applicant indicates that no data can be found in literature regarding the demonstration of prevention of PPH with uterotonic agents. At the same time reference is made to papers in which efficacy of oxytocin and active management of the third stage of labour (AMTSL) vs. expectant management, in which an advantage was shown with oxytocin over no prophylaxis in AMTSL.

Instead, the applicant has further elaborated on positive effects of misoprostol versus placebo in more severe outcomes evaluated in their study, i.e. Hb < 7 and 8 g/dL and provided additional analyses in which all women were enrolled, including those from the pilot phase that had been excluded due to invalid data collection, and a subgroup of women who did not receive iron supplementation. However, the relevance of these additional post hoc analyses is difficult to assess and does not solve the major issue that the robustness of results obtained in the single

published study in support of this indication is considered insufficient due to considerable problems in its conduct and questionable outcomes.

Based on above, the alternative justification regarding what is considered as a clinically meaningful effect of preventive treatment versus no prevention is considered not acceptable even though misoprostol has recently been included in the list of essential medicines for use in the prevention of PPH.

Prevention of heavy blood loss in women delivering at home in rural areas could be helpful from a public health perspective, but the applicant has not provided a valid argument in public health perspectives to what extent the predefined 35% reduction in blood loss would be beneficial and in which women. Additionally, the methodological issues identified with study HMP61203 do not provide reassurance regarding the use of misoprostol in home settings; there were problems with administration of misoprostol: in one case an overdose was given by the traditional birth attendant and also inadequate training was identified as an issue. In addition, the potential for off-label and incorrect use of misoprostol remains a cause for concern. It is therefore considered that the results of study HMP61203 do not provide adequate evidence of the benefit of home administered misoprostol in the prevention of PPH. The potential risk of off-label use and the risk of cardiovascular events should also be taken into account (see sections 2.6 and 2.8)

In conclusion, the results of this single study in support of the indication 'prevention of PPH' are considered insufficient in showing a relevant advantage of prevention of PPH with misoprostol over placebo when used by untrained or trained traditional birth attendants in settings where active monitoring of the 3rd stage of labour (AMTSL) is not practiced. This means that presenting misoprostol to all women in 3rd stage of labour to prevent PPH, regardless of the presence of proper guidance and care during labour is considered not adequately documented.

Consequently, the opinion of the applicant that "*Hemoprostol should be part of basic kits for maternal care in developing countries. In addition, given its excellent safety tolerance, and the absence of contraindication to the use for treatment and prevention of PPH, it should be made available without medical prescription and be distributed by nurses, midwives, traditional birth attendants. In addition, given the absence of specific storage conditions, Hemoprostol packs should be available in local hospital or dispensaries, and even provided to the woman for keeping at home in case of home delivery*." is not acceptable on the basis of the results of this single study.

It is noted that this is also the current opinion of the WHO (2012) in the prevention of PPH with misoprostol that "Systematic advanced provision of misoprostol necessitates additional research and cannot be recommended".

Following the CHMP recommendation that the indication "Prevention of post-partum haemorrhage" was not approvable due to major objections, the MAH withdrew this part of the indication at Day 180. The assessment report with regard to the prevention indication therefore represents the discussion at stage Day 180.

2.6. Clinical safety

Patient exposure

During the three pivotal studies (reports HMP061201, HMP061202 and HMP061203), 1,428 women have been exposed to Gymiso/Hemoprostol for PPH treatment or prevention in a single administration.

In addition, the applicant refers to a large additional number of women treated using Gymiso / Hemoprostol for treatment or prevention of PPH in studies that have been performed in developed countries in Africa, Asia or Latin America, mostly in poor rural populations. However, the collection of the safety data from these studies is not clear and therefore it is not possible to assess whether the safety data were collected in an appropriate way. Therefore, the safety assessment is focussed on the 3 pivotal published studies only.

Adverse events

Treatment of post partum haemorrhage:

Shivering and fever were the most frequently reported adverse events and their frequency was significantly higher in women given Hemoprostol than in those given oxytocin.

Unlike the use of misoprostol in other indications, the effects on body temperature are the main adverse events noted in the indications related with post-partum haemorrhage; in study HMP061202 i.e. shivering and fever is reported in about 50% of patients, and fever ≥ 40 ^{0}C reported in 13%. These adverse events were considered intolerable by about half of the patients suffering from this adverse event, pointing out that this adverse event has major impact on the women. Fever and shivering are described in the SmPC section 4.8 Summary of safety profile.

In study HMP061201 the percentages of women reporting adverse events of fever and shivering were somewhat lower but still considerable.

These adverse events are reported in public literature to be transient and short lived.

In the studies HMP061201 and HMP061202, side effects were detected by providers or reported by women within the first 20 minutes of treatment administration. Delivery attendants rated the severity. Side effects necessitating treatment were managed according to each hospital's clinical protocol. Fever was measured with standard thermometers routinely used in each centre. At three hours post-partum, delivery attendants re-assessed the health status of the woman. Prior to discharge from the hospital, delivery attendants interviewed women about the acceptability of side effects following treatment.

Following the first report of body temperature ≥40.0 C, delivery attendants were re-trained in recognizing, measuring, and managing fever.

An overview of adverse events from studies HMP 061202 and HMP 061201 is presented in the tables below:

Table 13: Study HMP061202 (women not exposed to oxytocin during labour):

Table 2.7.4-1 Safety information reported in study HMP061202

	misoprostol n = 488	oxytocin n = 490	RR (95% CI)	p-value
Shivering	229 (46·9)	82 (16·8)	2·80 (2·25–3·49)	<0·0001
Participants reporting shivering as intolerable	55 (11·3)	1 (0·2)	55·2 (7·7–397·5)	<0·0001
Fever	217 (44·5)	27 (5·5)	8·07 (5·52–11·8)	<0·0001
Participants reporting fever as intolerable	45 (9·2)	0 (0)	-- --	<0·0001
Temp ≥40·0 C°	66 (13·5)	0 (0·0)	-- --	<0·0001
Participants reporting high fever as intolerable	21 (4·3)	0 (0)	-- --	<0·0001
Nausea	49 (10·0)	41 (8·4)	1·20 (0·81–1·78)	0·213
Participants reporting nausea as intolerable	0 (0)	0 (0)	-- --	--
Vomiting	24 (4·9)	7 (1·4)	3·44 (1·50–7·92)	0·001
Participants reporting vomiting as intolerable	1 (0·2)	0 (0)	-- --	0·499
Fainting	4 (0·8)	4 (0·8)	1·00 (0·25–3·99)	0·635
Participants reporting fainting as intolerable	0 (0)	0 (0)	-- --	--
Diarrhea	2 (0·4)	2 (0·4)	1·00 (0·14–7·10)	0·686
Participants reporting diarrhea as intolerable	0 (0)	0 (0)	-- --	--
Other	21 (4·3)	20 (4·1)	1·05 (0·58–1·92)	0·495
Participants reporting other side effect as intolerable	2 (0·4)	1 (0·2)	2·01 (0·18–22·1)	0·498

Table 14: Study HMP061201 (women received prophylactic oxytocin)

	misoprostol n = 407	oxytocin n = 402	RR (95% CI)	p-value
Shivering	152 **(37·3)**	59 **(14·7)**	2·54 (1·95 - 3·32)	·0000
% of participants reporting that shivering intolerable	17 (4·2)	1 (0·3)	16·79 (2·25 - 125·58)	·0003
Fever	88 **(21·6)**	59 **(14·7)**	1·47 (1·09–1·99)	·007
Temp ≥ 40°C	5 **(1·2)**	1 **(0·3)**	4·94 (0·58–42·09)	·111
% of participants reporting that fever intolerable	11 (2·7)	5 (1·2)	2·17 (0·76–6·20)	·215
Nausea	59 **(14.5)**	69 **(17·2)**	0·84 (0·61–1·16)	·177
% of participants reporting that nausea intolerable	4 (1·0)	0 (0·0)	--	·063
Fainting or feeling faint	58 **(14·3)**	58 **(14·4)**	0·99 (0·71–1·38)	·517
% of participants reporting fainting or feeling faint intolerable	0 (0·0)	0 (0·0)	--	--
Vomiting	19 **(4·7)**	10 **(2·5)**	1·88 (0·88–3·99)	·069
% of participants reporting that vomiting intolerable	2 (0·5)	1 (2·5)	1·98 (0·18–21·70)	·504
Diarrhea	5 **(1·2)**	3 **(0·8)**	1·65 (0·40–6·84)	·396
% of participants reporting that diarrhea intolerable	0 (0·0)	0 (0·0)	--	--
Other	14 **(3·4)**	12 **(3·0)**	1·15 (0·54–2·46)	·434
% of participants reporting that any other side effect intolerable	0 (0·0)	0 (0·0)	--	--

However, duration and time of onset of fever were not systematically recorded. In order to collect details associated with this side effect in Quito, Ecuador, the treatment centre where reports of high fever were most frequent, delivery attendants were asked to complete an

additional study form to document onset, duration, peak temperatures, and treatment of cases with high fever. Based on these post hoc data, the authors concluded that body temperatures peaked 1–2 hours post-treatment (30-60 minutes after peak plasma levels), and gradually declined over 3 hours. Fevers were transient and did not lead to any hospitalisation. Baseline characteristics were comparable among women who did and did not develop a high fever, except for known previous PPH and rapid placental expulsion (Durocher et al, 2010).

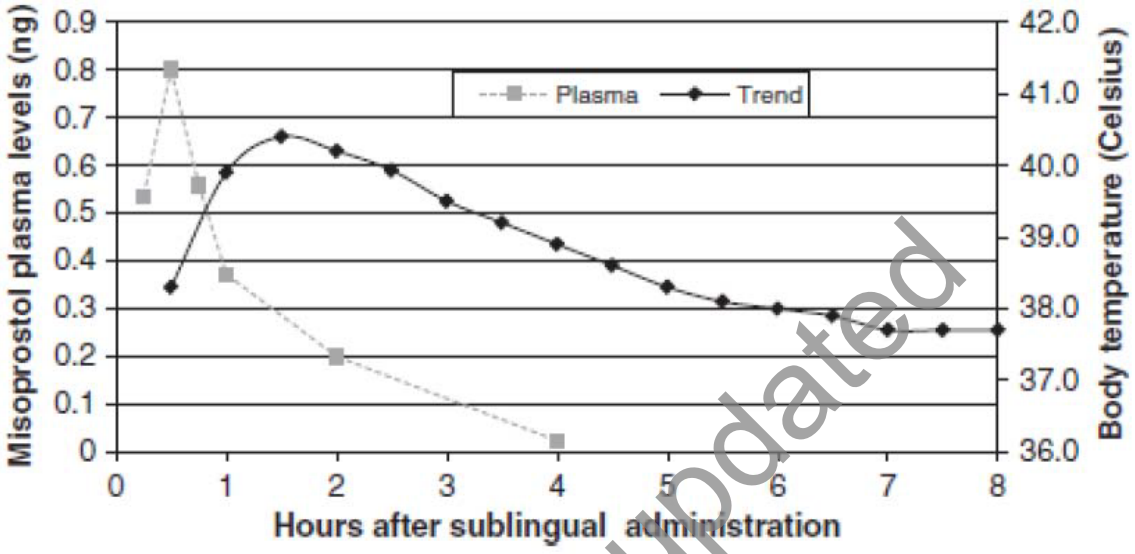


Figure 6 : Mean misoprostol plasma concentrations after sublingual administration of misoprostol (800 micrograms), and mean temperatures over time of 58 cases of high fever following treatment with 800 mcg sublingual misoprostol in Quito, Ecuador (Durocher et al, 2010)

Additionally, a pilot study conducted in the same centre in Quito in 2010 to determine whether a lower dose, 600mcg sublingual misoprostol (+oxytocin 10 mg prophylaxis) would result in a lower incidence of high fever (≥40°C). Rates of shivering and fever with 600mcg sublingual regimen were compared to previously documented rates in Ecuador following PPH treatment with 800mcg sublingual misoprostol. Results are presented in the table below.

Table 15:

Table 1 Side effects reported by delivery attendants among Ecuadorian women given PPH treatment with sublingual misoprostol (600mcg and 800mcg) *

	600 mcg(n = 50)	800 mcg(n = 163)	RR 95% CI
Any fever	44 (88.0)	151 (92.6)	0.95 (0.85-1.06)
≥ 40.0°C	8 (16.0)	58 (35.6)	0.45 (0.23-0.88)
Any shivering	48 (96.0)	146 (89.6)	1.07 (0.99-1.16)
Severe shivering	1 (2.0)	19 (11.7)	0.17 (0.02-1.25)
Any fainting	2 (4.0)	4 (2.5)	1.63 (0.31-8.64)
Any nausea	0 (0.0)	8 (4.9)	--
Any vomiting	0 (0.0)	8 (4.9)	--
Any diarrhea	0 (0.0)	2 (1.2)	--
Any delirium or altered sensorium	0 (0.0)	10 (6.1)	--
Any other side effect ^	1 (2.0)	10 (6.1)	0.33 (0.04-2.48)

* Values are given as n (%) unless stated otherwise.
^ 600mcg dose -- headache (1); 800mcg dose -- headache (2), thirst (3), pain/cramping (3), excessive sweating (1), Feel cold/teeth chattering (1)

Figure 7, in which data from both the post-hoc and pilot study are included, shows a similar pattern in time, but a dose-dependent effect on frequency of shivering and fever.

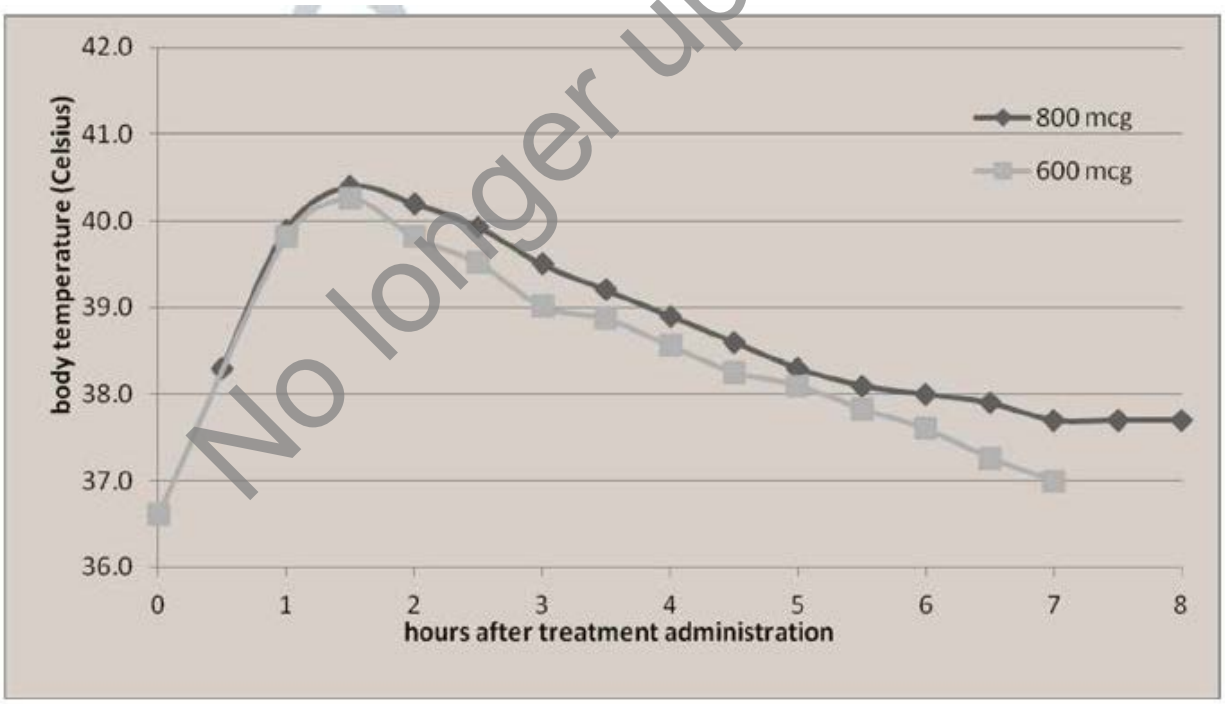


Figure 7: Average temperature for cases with high fever following 600mcg (n=8) and 800mcg (n=58) doses of misoprostol for PPH treatment

Convenience of sublingual administration

Regarding the convenience of sublingual administration of 4 tablets to be melted under the tongue for 20 minutes, the applicant indicated that providers who were asked to document any problems in administering misoprostol sublingually, reported few reports of problems with sublingual administration, but data were not presented. Additionally, the applicant indicated that 95% of women reported the sublingual mode of administration as acceptable or had a neutral response when asked to confirm the acceptability of the mode of administration (Blum 2010 (702), Winikoff 2010 (703)). However, in these publications, which were the basis of this application, details were not provided: "*Women reported that both treatment administrations (sublingual tablets and intravenous treatment) were acceptable (data not shown).*" These data were submitted in response to the CHMP List of outstanding issues and did not include a signal of difficulties with sublingual administration.

Prevention of post-partum haemorrhage

The most commonly reported adverse events were shivering and fever, but their incidences were lower than noted for treatment of PPH. Although it is not stated whether the adverse event collection is comparable in all studies, this outcome points out that oral administration and possibly a lower dose might be preferable.

Table 16

Table 2.7.4-3 Reported adverse events of study HMP061203

	Misoprostol (n = 533)	Placebo (n = 583)	*P* value*
Adverse effects reported			
▪ Nausea	8 (1.5%)	8 (1.4%)	0.527
▪ Vomiting	3 (0.6%)	3 (0.5%)	0.614
▪ Diarrhea	1 (0.2%)	0 (0.0%)	0.478
▪ Shivering	50 (9.4%)	23 (3.9%)	<0.0001
▪ Chills/cold	53 (9.9%)	29 (5.0%)	<0.0001
▪ Fever	4 (0.8%)	7 (1.2%)	0.326
▪ Headache	6 (1.1%)	7 (1.2%)	0.566
▪ Weakness/fatigue	9 (1.7%)	8 (1.4%)	0.425
▪ Dizziness/fainting	9 (1.7%)	6 (1.0%)	0.244
Referrals			
Woman referred for higher level of care			
▪ Multiple reasons possible	9 (1.7%)	10 (1.7%)	0.579
▪ Due to PPH	2 (0.4%)	3 (0.5%)	0.542
▪ Due to retained placenta	7 (1.3%)	7 (1.3%)	0.538
Maternal death	0 (0.0%)	0 (0.0%)	–

Safety information obtained from literature for treatment and prevention of PPH

Women who receive misoprostol during the third stage of labour are at risk for elevated body temperature, shivering, nausea and vomiting. The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia (317). Studies on postpartum use of misoprostol show the rates of shivering and fever to be drug-related, and to be dose- and route-dependent (317; 338).

Compared to placebo, a recent meta-analysis shows that the risk of pyrexia is increased three-fold with 400 mcg misoprostol and six-fold with 600 mcg misoprostol when administered during the third stage of labour (312). Higher rates of shivering and elevated body temperature are also associated with oral and sublingual routes of administration, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration (334; 906; 342).

One prevention trial comparing an oral misoprostol versus rectal administration of 600 mcg confirmed that the oral dose resulted in significantly higher rates of shivering (76 versus 54%) and fever (9 versus 1%) (329). Moreover, reported rates of shivering and fever vary greatly in the literature (343; 309). For example, rates of shivering and fever following a treatment dose of sublingual misoprostol (800mcg) given sublingually range from 7 to 90% and 5 to 93%, respectively (309). A review of the literature confirms that these side effects are transient, short-lived and not life threatening (310; 343; 341; 340; 309).

Two studies testing a 600 mcg regimen of sublingual misoprostol versus placebo as an adjuvant therapy also report that shivering and fever occurred significantly more often among women randomized to misoprostol (331; 330, both using Gymiso/Hemoprostol). Lower rates of shivering and fever were documented in one study testing 600 mcg (200 mcg orally + 400 mcg sublingually) among 160 women randomized to receive either misoprostol + standard uterotonics or placebo + standard uterotonics (shivering 29% vs. 10%; fever 20% vs. 10%) (328).

In conclusion, these additional data in literature indicate that the effects on body temperature are dose-related, but also related to the route of administration; sublingual administration showing higher rates compared to oral administration, and the lowest rates are noted with vaginal and rectal administration. These adverse events are reported to be transient and short-lived.

Long-term safety in treatment and prevention of PPH

Data on follow-up after discharge have not been collected in the treatment study. A separate study that was carried out in Quito, Ecuador, following completion of the two treatment studies presented in this application, has provided additional information on the existence of any prolonged adverse effects (León et al 2012 (308)). This study tested 600mcg of sublingual misoprostol for the treatment of primary PPH with the main objective to document the occurrence of side effects in this population that appears to be more sensitive to misoprostol´s thermoregulatory effects. Systematic body temperatures were measured for all women treated with 600 mcg sublingual misoprostol and confirmed a rate of 16% of high fever ≥40.0°C (8/50) in this population. Women with high fever were contacted by study staff one-week following hospital discharge to interview them about they were feeling. Women did not report any problems during their phone follow-up interview.

In the PPH prevention study HMP061203, women were followed up within 24 hours of the receipt of the medication by a trained Lady Health Visitor and again at 3-5 days postpartum for the collection of the Hb measure. No additional safety issues were reported.

Discontinuation due to AES

No discontinuations were reported.

Serious adverse events and deaths

Deaths:

In the studies where Gymiso/Hemoprostol has been used for treatment or prevention of PPH, three deaths were reported in women exposed to misoprostol (two in Widmer et al. study (330), one in the pivotal study HMP061201) and two deaths in women exposed to oxytocin (one in HMP061201 study) or placebo (one in Derman et al. study (307)).

- In the HMP061201 study, one woman allocated to misoprostol had disseminated intravascular coagulation, severe anaemia, and signs of shock after delivery. Hysterectomy was done, but she died the next day.
- In the HMP61201 study, one women allocated to oxytocin had an atonic uterus and developed severe postpartum haemorrhage one half hour after delivery. There was no response to any treatment (study drug, other uterotonic drugs and blood). Hysterectomy was performed 2.5 hours after delivery. Cardiac arrest occurred twice during the operation and the patient was resuscitated. Death occurred in the operating theatre after hysterectomy and a third cardiac arrest.
- In the Widmer et al. study (330) one woman was diagnosed with severe PPH that was unresponsive to misoprostol treatment and she died of disseminated intravascular coagulopathy on the day of delivery. The other woman was diagnosed with PPH that was suspected to be due to uterine atony. She received a blood transfusion and a laparotomy was done under general anaesthesia at which time a spiral tear of the left lateral wall of the uterus was identified and repaired and uterine artery was ligated. She was admitted in intensive care unit and died the next day from multiple organ failure.

The cases of death reported in patients treated with misoprostol are thought to be associated with complications of delivery or bleeding and not associated with misoprostol.

<u>Non-fatal serious adverse events:</u>

- Possible allergic reaction. Event 15 minutes after Oxytocin 10 IU IM prophylaxis, after treatment patient recovered.
- Hyperthermia. After PPH treatment, patient experienced hyperthermia (41.2˚C) and exhibited neurological signs. Temperature fell to 38˚C after approximately 2 hours. The patient recovered and was discharged in good health.

- Hospitalization/hysterectomy
    - Following delivery, the patient exhibited excessive bleeding believed to be a result of uterine atony, but bleeding was due massive uterine tear. Hysterectomy was performed and the patient recovered.
    - Following delivery, PPH due to atony was diagnosed at 700 cc, and treatment was administered immediately. Bleeding was controlled within 20 minutes. However, 40 min after treatment, bleeding restarted. Additional treatments were given. Fluids and blood transfusions (6 U) were started immediately with no improvement in condition. Hysterectomy was performed, patient recovered.
    - Following delivery PPH was diagnosed at 1300 ml blood loss and patient received study treatment. As active bleeding did not stop within 20 minutes, woman was given 400 mcg misoprostol and artery ligation was performed as standard treatment at the hospital. In addition, laparotomy and hysterectomy were performed and patient recovered.
    - PPH was diagnosed at 700 ml blood loss and patient received study treatment. Active bleeding did not stop within 20 minutes. Despite additional intervention, she exhibited disseminated intravascular coagulation, severe haemorrhage, and signs of shock. Laparotomy and hysterectomy were performed and patient recovered.

Fever ≥ 40^0C reported in public literature:

In several PPH prevention and treatment studies, misoprostol has been associated with fever greater than 40.0°C. One early case involved a reported peak temperature of 41.9°C following administration of oral misoprostol (800 mcg) given prophylactically (318). Other cases of high fever noted in the literature include five of 9,198 cases reported from the largest hospital- based clinical trial on the prevention of PPH, in which a prophylactic oral dose of 600 mcg misoprostol was used (336). Four cases of 1026 were reported in another study after testing a similar regimen (341). A PPH treatment trial in South Africa reported three women (out of 114) with temperatures of above 40.0°C following 1000 mcg misoprostol (200 mcg orally + 400 mcg sublingually + 400 mcg rectally) (311). There have been no other reports of high fever following rectal administration of misoprostol for PPH (317; 339). In Pakistan, a single case of high fever (out of 29) following adjunct treatment with a sublingual dose of 600 mcg was reported (331). A multi-country trial investigating the adjunct use of sublingual misoprostol (600 mcg) following standard uterotonics for PPH treatment also documented a 7% rate of high fever above 40.0°C among 48 women (out of 704), compared with a rate of 1% among women who received standard uterotonics + placebo to treat their PPH (330). However, information on these adverse events regarding time of onset, duration, treatment emergent or not is absent.

Cardiovascular events:

Cardiovascular events (such as myocardial infarction and cerebrovascular events) are considered a class effect of prostaglandin analogues and reported in other gynaecological indications, and have been reported to occur during use with misoprostol in other gynaecological indications, but

no cardiovascular or cerebrovascular events associated with misoprostol for PPH were reported in the data reviewed for this application. Additionally, no studies have documented these events. Nevertheless, a warning is included in the SmPC that "*Cases of cardiovascular events associated with misoprostol have been reported. The possibility of occurrence of a cardiovascular event should be considered in women with pre-existing cardiovascular risk factor(s)*.". These events will be subject to post-marketing surveillance.

Based on literature review, results of clinical trials and commercial experience of dedicated misoprostol for pregnancy termination, no class effects other than cardiovascular risks are anticipated with the use of misoprostol at the proposed regimens in the claimed indications (treatment and prevention of PPH).

Laboratory findings

There are no reported laboratory tests for safety in literature and none were performed in pivotal studies. Therefore, only measurement of Hb values as part of efficacy measures was performed. According to the applicant, this was due to the short duration of treatment (single dose), and the context of use of misoprostol. The CHMP accepted the applicant`s clarification.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with Hemoprostol.

Interaction data available from Gymiso showed that the pharmacokinetics of propranolol and diazepam are not influenced by concomitant administration of misoprostol. Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

In a pivotal study performed with HEMOPROSTOL, no adverse events which would suggest the existence of an interaction between misoprostol and oxytocin were reported in women exposed to prophylactic oxytocin, either intramuscular or intravenous prior to administration of Hemoprostol.

Concomitant use with non steroidal anti-inflammatory drugs may reduce the efficacy of misoprostol; if analgesia is necessary, it is preferable to use paracetamol-type analgesics.

This information has been reflected in the Product information.

Post marketing experience

Hemoprostol is not licensed anywhere. However post-marketing data available from Gymiso in the pregnancy termination indication were presented:

Safety information is presented for Gymiso for a different indication (medical termination or pregnancy in combination with mifepristone and cervical ripening prior to endouterine procedure). Gymiso has been commercialized in France since 2003. Up to 2011, the total patient exposure has been 164,210.

The safety information of the currently approved Gymiso SmPC (2009) is as follows:

The most frequent undesirable effects which are observed during treatment with misoprostol are the following:

- *Gastrointestinal disorders*: nausea (transient and mild), vomiting, diarrhoea, abdominal pain
- *Cardiovascular events* in total 12 serious cardiovascular events were reported.
- *Reproductive system disorders*: very frequent uterine contractions observed in the hours following misoprostol intake; vaginal bleeding, sometimes heavy and prolonged when used with mifepristone for medical termination of pregnancy (see SmPC section 4.4, Special warnings and special precautions for use).
- *General disorders*: headache, dizziness and, more rarely, chills and fever.

Because of castor oil presence as excipient, digestive symptoms (nausea, vomiting, abdominal pain) can be observed.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the AE profile of misoprostol used in the post partum indications is dominated by adverse events related to body temperature; fever up to or even higher than 40ºC, chills, shivering, and this has been reflected in the SmPC. The method of recording body temperature, the intensity, duration, time of onset and the need for treatment are sufficiently documented, although the larger part of specific data on pattern of fever and other adverse events came from a study performed after both PPH treatment studies were completed. Nevertheless, the newly discussed data from literature review support the events related to fever to be dose-dependent, transient and short-lived. Regarding other adverse events, mainly of gastrointestinal origin, the incidence was low and comparable with that of oxytocin. Long-term adverse effects were not noted. Though cardiovascular events are considered a class effect of prostaglandin analogues

and reported in other gynaecological indications, no cardiovascular or cerebrovascular events associated with misoprostol for PPH were reported. Nevertheless, a warning is included in the SmPC that "*Cases of cardiovascular events associated with misoprostol have been reported. The possibility of occurrence of a cardiovascular event should be considered in women with pre-existing cardiovascular risk factor(s)*". These events will be subject to post-marketing surveillance.

Based on literature review, results of clinical trials and experience from marketed misoprostol use (in pregnancy termination), no class effects other than cardiovascular risks are anticipated with the use of misoprostol at the proposed regimens in the claimed indications (treatment and prevention of PPH).

Regarding the non-prescription status as proposed by the applicant, the CHMP considers the potential for off-label and incorrect use of misoprostol as a concern, especially in the prevention of PPH indication. Since the latter indication has been withdrawn, this concern will be less relevant as primarily medical staff and trained suppliers will be involved in the treatment of PPH. These concerns are addressed in the RMP.

The safety profile has been reflected in the product information and is discussed in the risk management plan.

The CHMP recommends that the Scientific Opinion Holder shall submit yearly periodic safety update reports for this product, until otherwise agreed by the CHMP. The Scientific Opinion Holder shall submit the first periodic safety update report for this product within 12 months following Scientific Opinion.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Having considered the Risk Management Plan version 3 within the context of the application under the legal basis of Article 58 of Regulation (EC) No 726/2004, the PRAC considers by consensus decision that the risk management system for misoprostol (Hemoprostol)" indicated in women of childbearing age for treatment of Post-Partum Haemorrhage due to uterine atony in situations where intravenous oxytocin is not available" is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 17: Summary of the Safety Concerns

Identified risk	Fever and related events (chills, shivering)
Potential risk	Off-label use for labour induction Off-label use for pregnancy termination Incomplete abortion in the context of off-label use for pregnancy termination Congenital abnormalities in the context of off-label use in early pregnancy Misuse for illegal purposes in case of "not subject to prescription" status Cardiovascular events Breastfeeding
Missing information	Use in children Women with renal or hepatic comorbidities
Pharmacological class effect	Prostaglandin class effects

The PRAC agreed.

- **Pharmacovigilance plans**

Considering that the application is submitted under the legal basis of Article 58 of Regulation (EC) No 726/2004 and consequently, the medicinal product is intended exclusively for markets outside the European Union, the PRAC acknowledged the potentially very heterogeneous health care settings in the regions (which are currently unknown) where the product is intended to be used/marketed on the basis of the Scientific Opinion of the CHMP and therefore expressed some limitations to conclude on some additional pharmacovigilance activities to be performed by the applicant that could be implemented homogeneously in all relevant countries. However, since off-label use for labour induction, pregnancy termination and any other misuse are considered important issues the applicant is encouraged to monitor these issues at national level where possible, in particular with national authorities, local distributor(s) and in co-operation with international non-governmental organisations, as appropriate.

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 18: Summary table of Risk Minimisation Measures

Safety concern	**Proposed Pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Important identified risk		
Fever and related events (chills, shivering)	Routine pharmacovigilance (PV) Special attention in PSUR	SmPC section 4.8
Important potential risk		
Off-label use for labour induction	Routine PV Activities Special attention in PSUR	Black-box on PL and outer carton
Off-label use for pregnancy termination	Routine PV Activities Special attention in PSUR	SmPC section 4.3: "Ongoing pregnancy"
Incomplete abortion in the context of off-label use for pregnancy termination	Routine Pharmacovigilance Special attention in PSUR	-
Congenital abnormalities in the context of off-label use in early pregnancy	Routine PV Activities Special attention in PSUR	SmPC section 4.6
Misuse for illegal purposes in case of "not subject to prescription" status	Routine PV Activities Special attention in PSUR	-
Cardiovascular events	Routine PV Activities Special attention in PSUR	SmPC section 4.4
Breastfeeding	Routine PV Activities Special attention in PSUR	SmPC section 4.6

Missing information		
Use in children	Routine PV Activities Special attention in PSUR	SmPC section 4.2
Women with renal or hepatic comorbidities	Routine PV Activities Special attention in PSUR	SmPC section 4.4
Pharmacological class effects		
Risks related to the use of prostaglandin	Routine PV Activities Special attention in PSUR	SmPC section 4.3

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

In addition, the PRAC recommends the Applicant to explore and support training and monitoring programs organised with local distributor(s) and/or NGO(s).

PRAC also recommends that the labelling of the product should contain on the outer box a nationally adapted pictogram to stress that Hemoprostol should not be used during pregnancy.

The CHMP endorsed this advice without changes.

2.9. User consultation

The applicant has not submitted results of user testing. User testing of the Package Leaflet is not mandatory because the product is to be marketed outside the European Union.

3. Benefit-Risk Balance

Benefits

Hemoprostol contains 200 mcg misoprostol, a synthetic analogue of prostaglandin E1; its pharmacodynamic property in the reproductive tract is increasing uterine contractility.

This application was submitted in accordance with Article 58 of (EC) No Regulation 726/2004 to the EMA for a scientific opinion in the context of cooperation with the World Health Organisation.

Hemoprostol will exclusively be intended for markets outside the Community. The gold standard for prevention and treatment of Post Partum Haemorrhage (PPH) associated with uterine atony is oxytocin. However, in low resource countries oxytocin is not always available (oxytocin requires cool storage conditions) or feasible (requires IV administration).

At the start of the procedure, the applicant proposed the following indication and posology

*"HEMOPROSTOL 200 microgram tablets are indicated in adults of childbearing age for **treatment** and **prevention** of Post-Partum Haemorrhage".*

- Treatment of Post-Partum Haemorrhage:
  *The treatment consists of four tablets (800 micrograms) to be taken in a single **sublingual** intake.*
  Place the four tablets of HEMOPROSTOL under the tongue and let them melt for 20 minutes.
- Prevention of Post-Partum Haemorrhage:
  *The treatment consists of three tablets (600 micrograms) to be taken in a single **oral** intake.*

During the procedure the second part of the indication, i.e. Prevention of PPH, has been withdrawn by the applicant due to unsolvable major issues related to the efficacy and safety of misoprostol with regard to the prevention indication. Therefore only the benefit-risk balance of the indication Treatment of PPH is discussed.

Beneficial effects in the Treatment of PPH

To document efficacy for this part of the indication, two published Phase III studies (HMP061202 and HMP061201) were submitted. The studies were performed by Gynuity, an organisation sponsored by the Bill and Belinda Gates foundation with supply of the tablet by the applicant.

Both studies selected two identical primary efficacy endpoints, i.e. cessation of bleeding within 20 minutes and amount of blood loss of at least 300 ml, but only for the first endpoint a non-inferiority margin, i.e. a margin of 6%, and sample size calculation was performed

Study **HMP061202** in ***women who have not received oxytocin prophylactically*** during the third stage of labour:

Outcome co-primary efficacy endpoints (results) are as follows:

1. The success rate (defined as percentage of women in whom active bleeding stopped within 20 minutes of initial treatment) in the misoprostol arm was 90% and in the oxytocin arm was 96% (relative risk 0.94, 95% CI 0.91–0.98). The crude difference was 5.3% (95% CI 2.6 – 8.6).
2. Additional blood loss of at least 300 mL after treatment occurred for 30% of women receiving misoprostol and 17% of women receiving oxytocin (relative risk 1.78, 95% CI 1.40–2.26). The crude difference was not presented.

Although non-inferiority versus oxytocin could not be established, the effect size in the misoprostol group is considered adequate such that efficacy can be concluded. It is considered that 90% is incontrovertibly a positive effect which, if this was an uncontrolled trial, would be acceptable especially within the context of post-partum haemorrhage where the effects can lead to severe morbidity and mortality.

In the second study **HMP061201** performed in ***women who have received oxytocin*** prophylactically during the third stage of labour, non-inferiority was proven for the first primary endpoint (89% in the misoprostol arm and 90% in the oxytocin arm). The results for the second primary endpoint of additional blood loss suggest misoprostol is similar to oxytocin, as the relative risk is close to 1. However, the population selected in this study is not comparable with the population aimed for, as the intended population is unlikely to have access to oxytocin at all. Additionally, the prophylactic use of oxytocin may have rendered the study insensitive to detect differences between misoprostol and oxytocin.

Supportive evidence was found from literature review. A RCT by G Walraven et al[15] where misoprostol was compared to placebo suggested that additional blood loss greater than 500ml is lower in the misoprostol group when compared to placebo (16.5 versus 28.4%).

Uncertainty in the knowledge about the beneficial effects - Treatment of PPH

Clinical

- The population selected in the study HMP061201 is not comparable with the population aimed for, as women were routinely prophylactically treated with oxytocin in the 3rd stage of labour as part of active management of third stage of labour measures. The population aimed for would not have access to oxytocin. This population may also differ from the other study in which no prophylactic treatment was given, so definite conclusions cannot be drawn and this study is considered as supportive only.
- Although it can be reasonably assumed, based on the latest papers on causes of maternal death [16,17,18,] that in the absence of medical treatment the morbidity and mortality of PPH will be considerable, an estimation of the potential of misoprostol for saving lives through providing a treatment option in life-threatening bleedings, where no other treatment options are available, in the settings of countries covered by WHO ART, would have been helpful.
- In both treatment studies, misoprostol was administered in a hospital setting (secondary-level and tertiary-level facilities). Subsequently, while the applicant considered that misoprostol should not be subject to medical prescription, the benefit-risk balance of the non-prescription status could not be assessed. Furthermore, advanced purchase of misoprostol would not be justified for treatment of PPH; and the CHMP recommends Hemoprostol to be subject to medical prescription.In every instance, it is anticipated that dispensation of the product will be regulated at national level because not only medical staff, but also midwives or birth attendants are mentioned as potential administrators of Hemoprostol. Therefore, the dispensation and training of this non-medical group of suppliers of the product should be adequately regulated, taking into account the safety concerns discussed in the RMP; the appropriate tools are to be agreed with the national regulatory authorities.

Clinical statistics

[15] Gijs Walraven, Yusupha Dampha, Bubacarr Bittaye, Maimuna Sowe Justus Hofmeyer. Misoprostol in the treatment of postpartum haemorrhage in addition to routine mamagement: aplacebo randomised controlled trial

[16] *Khalid S, Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367: 1066–74.*

[17] *Ramanathan G, Arulkumaran S. Postpartum hemorrhage.J Obstet Gynaecol Can 2006; 28: 967–73.*

[18] *AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003; 67: 1–11.*

For the two studies provided there were deficiencies in the information on the pre-specified statistical methodology provided. Despite this, the CHMP considered the data to be adequate in order to draw conclusions on the results.

Risks

The safety data from studies in both indications are relevant to the risks and are therefore included in the discussion on risks.

Unfavourable effects in the treatment and prevention of PPH

During the three pivotal studies (reports HMP061201, HMP061202 and HMP061203), 1,428 women have been exposed to Gymiso/Hemoprostol for PPH treatment or prevention in a single administration. The collection of safety data is limited as no safety measurements were performed, except for Hb measurements.

The safety profile of misoprostol is less favourable than noted for oxytocin. Unlike the use of misoprostol in other indications, the effects on body temperature, i.e. shivering and fever, are the main adverse events noted in the indications related with post partum haemorrhage and their frequency was high, while in the oxytocin groups this specific adverse event was hardly reported. In study HMP061202 shivering and fever is reported in about 50% of patients, and fever ≥ 40ºC reported in 13%. These adverse events have major impact on the women. This type of adverse event is reported in literature to be related to the dose but also to the route of administration. In several PPH prevention and treatment studies, misoprostol has been associated with fever higher than 40.0°C when using doses between 600-1000 sublingually. Additional safety data submitted indicate that the effects on body temperature are related to the dose administered and the route of administration; most common with the sublingual route while the lowest rates are noted with vaginal and rectal administration. These adverse events have been demonstrated to be transient and short-lived.

Other adverse events frequently reported included gastro-intestinal adverse events like nausea, vomiting, and diarrhoea of which the frequency was comparable between misoprostol and oxytocin groups.

Postmarketing safety data available for other indications of misoprostol in France:

The most frequent undesirable effects which are observed during treatment with misoprostol in the indications "*medical termination or pregnancy in combination with mifepristone*" and "*cervical ripening prior to endo-uterine procedure*" include gastrointestinal disorders: nausea (transient and mild), vomiting, diarrhoea, abdominal pain, and reproductive system disorders: very frequently uterine contractions were observed in the hours following misoprostol intake; vaginal bleeding, sometimes heavy and prolonged when used with mifepristone for medical termination of pregnancy. Twelve serious cardiovascular events were reported in relation to these indications, but there was no signal of cardiovascular events in the PPH indications.

Uncertainty in the knowledge about the unfavourable effects in the treatment and prevention of PPH

The collection of safety data is limited as no laboratory measurements were performed, other than Hb. Normally, complete chemistry, vital signs etc. are evaluated.

Though cardiovascular events have been reported to occur during use with misoprostol in other gynaecological indications, no cardiovascular or cerebrovascular events associated with misoprostol for PPH were reported. Additionally, no studies have documented these events. Nevertheless, a warning is included in the SmPC that "*Cases of cardiovascular events associated with misoprostol have been reported. The possibility of occurrence of a cardiovascular event should be considered in women with pre-existing cardiovascular risk factor(s)*.". These events will be subject to post-marketing surveillance.

The potential for off-label and incorrect use of misoprostol remains a concern, although less relevant since the prevention of PPH indication has been withdrawn. Primarily medical staff and trained suppliers will be involved in the treatment of PPH. This concern has been addressed in the risk management plan.

Benefit-risk balance

Importance of favourable and unfavourable effects in the treatment of PPH

The current gold standard in treatment and prevention of Post Partum Haemorrhage (PPH) is oxytocin which is administered IV. In the prevention of PPH, oxytocin is part of active management of the third stage of labour (AMTSL). From public literature it is known that the efficacy of misoprostol in the indication of treatment of PPH is less than noted for oxytocin. In the WHO recommendations and other guidelines, oxytocin is the preferred treatment when available and IV administration is feasible.

The data of the published study in treatment of PPH **HMP061202** (in which no prophylactic oxytocin was given in the 3rd stage of labour) showed efficacy on the endpoint 'active bleeding stopped within 20 minutes of initial treatment' of 90% in the misoprostol arm versus 96% in the oxytocin arm. Although non-inferiority versus oxytocin could not be established, the effect size in the misoprostol is such that efficacy can be concluded.

In the other study **HMP061201** in women who were given prophylactic oxytocin in the 3rd stage of labour, non-inferiority versus oxytocin was achieved on one of the two primary endpoints (89% versus 90% of women in whom cessation of active bleeding had stopped within 20 minutes), again demonstrating meaningful efficacy. However, the population selected in this study is not comparable with the population aimed for, as this population does not have access to oxytocin for whatever reason. Further, this design of pre-use of oxytocin may render the study insensitive to detect differences between misoprostol and oxytocin. Therefore, this study can be accepted as supportive only.

Although the statistical documentation is not considered optimal, the results of the studies are considered sufficiently adequate to draw conclusions.

Nevertheless, it can be reasonably assumed, based on the latest papers on causes of maternal death, [19],[20],[21] that in the absence of medical treatment the morbidity and mortality of PPH will be considerable with a poorer outcome than now seen in the two clinical studies with misoprostol.

Overall, the safety profile of misoprostol in the treatment of PPH was less favourable than noted for oxytocin, due to the effects on body temperature. TAE profile of misoprostol used in the post-partum indications is dominated by adverse events related to body temperature; fever up to higher than 40 ºC, chills, shivering, while this adverse event was hardly noted in the oxytocin groups. Additional data submitted on increased body temperature, i.e. intensity, duration, time of onset and the need for treatment indicated that these adverse events are transient and short lived. Regarding other adverse events, mainly of gastrointestinal origin, the incidence was low and comparable with that of oxytocin. Additionally submitted follow-up after hospital discharge indicated no long-term problems.

Discussion on the benefit-risk balance in the treatment of PPH

Although direct comparison to no treatment is lacking, the data reviewed support that misoprostol is effective in the treatment of post-partum haemorrhage to a clinically relevant extent - although less so when compared to oxytocin – with an acceptable safety profile provided that the recommendations in the product information and risk management plan are adhered. Therefore, it can be assumed that misoprostol may be beneficial in situations where oxytocin is not available for various reasons or cannot be administered due to its i.v. administration.

The conclusions on the benefit-risk balance of misoprostol administration in a hospital setting cannot be extrapolated to places outside of hospitals. Since the applicant has withdrawn the proposal to include prevention of post-partum haemorrhage in the indication Hemoprostol will only be used as a treatment of PPH, where it is likely that medical staff, midwives or birth attendants duly authorized to assist in delivery will be the primary persons allowed to deliver the product. The CHMP is of the opinion that advanced purchase of misoprostol is not justified for treatment of PPH; in principle, the CHMP recommends that Hemoprostol in the treatment of PPH is subject to medical prescription. In every instance, it is anticipated that dispensation of the product will be regulated at national level as not only medical staff, but also midwives or birth attendants are mentioned as potential administrators of Hemoprostol. Therefore, the dispensation and training of this non-medical group of suppliers of the product should be adequately regulated, taking into account the safety concerns discussed in the RMP;the appropriate tools are to be agreed with the national regulatory authorities.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Hemoprostol in the indication

[19] *Khalid S, Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367: 1066–74.*
[20] *Ramanathan G, Arulkumaran S. Postpartum hemorrhage.J Obstet Gynaecol Can 2006; 28: 967–73.*
[21] *AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003; 67: 1–11.*

"*Hemoprostol is indicated in women of childbearing age for treatment of Post Partum Haemorrhage due to uterine atony in situations where intravenous oxytocin is not available*" is favourable.

This opinion is based upon the risk-benefit scenarios on the populations and conditions of use as documented with clinical data by the applicant.

Recommendation regarding supply and use

CHMP recommends Hemoprostol to be subject to medical prescription.
It is ultimately the responsibility of the National Regulatory Authorities to decide on the adequate supply status.

Other recommendations and requirements of the Scientific Opinion Holder

- **Periodic Safety Update Reports**

The Scientific Opinion Holder shall submit the first periodic safety update report for this product within 12 months following Scientific Opinion (DLP 30 June 2014). Subsequently, the Scientific Opinion Holder shall submit yearly periodic safety update reports for this product, until otherwise agreed by the CHMP.

Recommendations or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Scientific Opinion Holder shall perform the required pharmacovigilance activities detailed in the agreed RMP presented in Module 1.8.2 of the Scientific Opinion Application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable

- **Recommendation to complete post-authorisation measures**

Not applicable

Recommendations or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.