Public Assessment Report
Scientific discussion

MISODEL
(misoprostol)

SE/H/1224/01/DC

This module reflects the scientific discussion for the approval of Misodel. The procedure was finalised at 2013-10-16. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Ferring Pharmaceuticals has applied for a marketing authorisation for Misodel, 200 micrograms, vaginal delivery system. The active substance misoprostol is a synthetic analogue of prostaglandin E1 (PGE1), a naturally occurring oxytocic compound. Prostaglandins initiate the process of cervical preparation or ‘ripening’ for delivery and sensitise the myometrium to oxytocin. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Misodel is presented in the form of a vaginal delivery system containing 200 micrograms of misoprostol. The excipients are a cross-linked hydrogel polymer (manufactured from macrogol, 1,2,6-hexanetriol and dicyclohexylmethane-4,4'-diisocyanate), butylated hydroxyanisole and a polyester retrieval system. The vaginal delivery system is packed in single foil sachet.

II.2 Drug Substance

Misoprostol has a monograph in the Ph Eur. The drug substance manufacturer has provided a CEP.

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

II.3 Medicinal Product

Misodel vaginal delivery system consists of a hydrogel polymer vaginal insert containing misoprostol. The insert is contained within a polyester retrieval system. Misodel vaginal delivery system is formulated using excipients described in the current Ph Eur, except for cross-linked hydrogel polymer which is controlled according to an acceptable in house specification. None of the raw materials used in the product are of human or animal origin.

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process has been described and validated. In-process controls, critical steps and holding times have been satisfactorily described and justified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in a freezer.
III. NON-CLINICAL ASPECTS

III.1 Introduction

Non-clinical data have been provided in the form of published literature, information obtained from studies with Cytotec®, and three new non-clinical studies in which misoprostol was administered to pregnant rats in the form of rat hydrogel polymer discs, or by oral gavage.

III.2 Pharmacology

Misoprostol is a synthetic analogue of prostaglandin E₁ (PGE₁). The pharmacological effects of prostaglandins are well-known and thus no new non-clinical pharmacology studies are considered necessary.

No primary or secondary pharmacodynamic studies have been conducted on the hydrogel polymer or retrieval system materials, since these are inactive materials, with no expected pharmacological activity. This is considered acceptable.

Safety pharmacology studies on misoprostol did not identify any major findings of concern. Transient hypotension and sedation are unlikely to occur at clinical doses. Diarrhogenic effects identified both non-clinically and clinically after oral administration of misoprostol were not seen by the vaginal route.

III.3 Pharmacokinetics

After oral ingestion, misoprostol is rapidly de-esterified to the biologically active misoprostol acid metabolite. The free acid interacts with gastrointestinal prostaglandin receptors, is absorbed, or is metabolized by gastrointestinal cells, the liver and other tissues. About 7% of the dose appears in the systemic circulation as misoprostol acid.

Rats were dosed on Day 17 of gestation with 10 or 30 mcg misoprostol (28 and 82 mcg/kg) by the vaginal route (polymer discs). Almost 100% of the administered dose was released within 8 hours. Systemic exposure to misoprostol acid was approximately 20- to 40 -fold higher than could be achieved by similar doses administered as a bolus dose by oral gavage.

The absorption pharmacokinetics differs between rats and humans, as indicated by lower exposure after oral dosing in rats. In women, intravaginal administration of misoprostol caused a 3-fold higher exposure as compared to administration by the oral route.

Tissue distribution data on misoprostol are very limited. Results from a study on a structurally related compound, dinoprostone, show extensive local exposure in the cervix/vagina, with considerably lower radioactivity levels in other parts of the reproductive tract, as well as in the fetus. Other organs showing significant radioactivity were the liver, lung, kidney and gastrointestinal tract. There was no indication of accumulation in any tissue.

Following oral ingestion, misoprostol acid is metabolized to inactive metabolites by fatty acid oxidizing (beta and omega oxidation) enzymes, present in organs throughout the body. The major route of excretion is via the urine. Since metabolism of misoprostol can take place in numerous tissues, it can be assumed that the routes of metabolism and excretion after
vaginal dosing are similar to those observed after oral administration. Although data is limited it is stated that misoprostol does not alter liver microsomal cytochrome P-450 concentrations or mixed function oxidase activities measured in vitro.

No animal studies investigating placental or milk transfer of misoprostol have been performed.

III.4 Toxicology

Single dose toxicity
The acute toxicity of misoprostol has been studied in rats, mice and dogs using various routes of administration. Oral LD₅₀ values in rodents were in the range of 27-138 mg/kg, while dogs were more sensitive (lowest lethal dose 10 mg/kg, providing a 1867-fold safety margin to the maximum anticipated human dose).

No formal acute toxicity study has been performed by intravaginal administration. In the comparative pharmacokinetic study in pregnant rats, no adverse effects on bodyweight, food consumption or survival of fetuses were observed at 82 mcg/kg (30 mcg/rat). No signs of local toxic effects in the cervix or vagina were observed. This dosage is about 27 times the maximum anticipated human dose of misoprostol (3 mcg/kg) that will be encountered during use of Misodel.

Repeated dose toxicity
Oral administration of misoprostol identified the gastrointestinal (GI) tract as target organ for toxicity in rats and dogs. The observed GI effects (diarrhoea, gastric epithelial hyperplasia, forestomach hyperkeratosis, increased stomach weights) were reversible and probably represent exaggerated pharmacology of misoprostol. In addition, increased serum iron levels and increased hemosiderin content in the liver were observed in rats. Since there were no indications of anemia, these findings are suggestive of an effect upon iron absorption.

Although no NOEL could be established for the histopathological changes in the stomach, dose levels of 0.16 mg/kg in the rat and 0.03 mg/kg in the dog may be regarded as NOAEL since no diarrhoea or other clinical signs were present at these dosages. Using the dog NOAEL after oral repeated dosing, the safety margin to the maximum anticipated human single vaginal dose of misoprostol (3 mcg/kg) that will be encountered during use of Misodel is about 6-fold.

Oral toxicity testing of the hydrogel polymer in rats and dogs showed no toxicity of the polymer at dosages several orders of magnitude above the maximum likely human exposure during use of Misodel. A 14-day vaginal study of hydrogel polymer in rats showed no treatment-related systemic or local effects up to 0.34 mg/rat/day.

The materials used to form the retrieval system of MVI were tested for vaginal irritation in rabbits for 14 days. No signs of systemic toxicity were observed.

Genetic toxicity
Misoprostol was negative in the Ames and MLA assays, as well as in the in vivo mouse micronucleus test, indicating lack of genotoxic potential. The hydrogel polymer was tested in vitro, including the Ames and MLA assays, with negative results.

Carcinogenicity
The carcinogenic potential of misoprostol was assessed in life time-studies using oral administration in mice (up to 16 mg/kg/day) and rats (up to 2.4 mg/kg/day). Treatment-related
Histopathological changes were seen in these studies (hyperplastic changes in the stomach of both species, hyperostosis in mice), but no evidence of any drug-related neoplastic findings were observed.

**Reproductive toxicity**
The effect of misoprostol on fertility was evaluated in the rat, using oral administration. At 1.6 mg/kg/day and above, the numbers of implantations and live fetuses were decreased, and doses of 1 mg/kg/day and above were associated with increased numbers of resorptions. NOAEL for the fertility effects of misoprostol was 0.4 mg/kg/day, providing a 20-fold safety margin to maximum anticipated human dose (3 mcg/kg).

No teratogenic effects of misoprostol were observed in rats at dosages up to 10 mg/kg/day. In rabbits, an increase in fetuses with extra ribs was observed at a dosage of 1.0 mg/kg/day, probably associated with maternal toxicity at this dose level. In mice, administration of a high single oral misoprostol dose (30 mg/kg) on Day 10 of gestation caused cleft palate and reduced skeletal ossification, as well as increased resorption rates.

In the peri/postnatal toxicity studies, slightly increased pup mortality and reduced pup growth rate were observed at 1.6 or 10 mg/kg/day, with 1.0 mg/kg/day being an overall NOAEL for peri/postnatal reproductive toxicity. This dosage was used in one of the new pharmacokinetic studies in rats (Study COP013), where exposure was measured. Extrapolating from this study, a 23-fold safety margin in terms of AUC can be derived, based on mean systemic exposure in clinical pharmacokinetic study Miso-Obs-205.

Intravaginal exposure of rats to 82 mcg/kg misoprostol (29-fold safety margin in terms of AUC) on Day 17 of gestation caused no effect on the number of viable fetuses or resorptions, as evaluated 48 h after administration.

In conclusion, administration of misoprostol to animals during early gestation and organogenesis clearly affects implantation and fetal survival, and also at high doses causes teratogenic effects. These effects are known to translate to humans, but are not considered to be of concern for the present application, since Misodel will be contra-indicated before week 36 of gestation i.e. it cannot be used in the first trimester.

**Local tolerance**
The local tolerance of misoprostol, the hydrogel polymer, and the polyester retrieval system, has been adequately examined in rats and rabbits. No adverse local effects of any of the components of Misodel have been observed.

**Other toxicity**
Some additional studies on the polyester retrieval material were performed, comprising cytotoxicity, hemolytic potential, pyrogenicity and sensitization studies on extracts of the material. All these studies were negative. In addition, a specific in vitro study examining the potential for the retrieval system material to produce Toxic Shock Syndrome Toxin-I (TSST-I) was conducted. This study showed that the retrieval system material did not affect growth of *Staphylococcus aureus* and reduced production of TSST-I by the organisms.

**Impurities**
A degradation product (8-iso-misoprostol) has been sufficiently toxicologically qualified.
III.5  Ecotoxicity/environmental risk assessment

Misoprostol has an experimental logK\text{ow} \equiv 3.4 which is below the limit of 4.5 for screening for persistence, bioaccumulation and toxicity according to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

The maximum daily dose consumed per inhabitant is 200 mcg misoprostol. This gives a PEC\textsubscript{SURFACEWATER} value of 0.001 mcg/L. As the PEC\textsubscript{SURFACEWATER} value is below the action limit of 0.01 mcg/L set forth in the guideline, and no other environmental concerns are apparent, this medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients. Thus, no additional testing is deemed necessary.

III.6  Discussion on the non-clinical aspects

The non-clinical evaluation of the active substance misoprostol and the vaginal delivery system used in Misodel is considered adequate. No major safety issues have been identified from a non-clinical point of view.

IV.  CLINICAL ASPECTS

IV.1  Pharmacokinetics

The pharmacokinetic data of misoprostol acid following administration of vaginal Misodel (duration 24 h) and oral Cytotec® was obtained in a study performed in 12 healthy non-pregnant volunteers (Figure 1). The plasma exposure in terms of AUC\text{inf} of misoprostol acid following oral dosing (200 μg) was significantly lower compared to vaginal administration (200 μg). The exposure (AUC\text{inf}; median (min-max)) was 375 (151-540) and 1009 (458-2059) pg·h/mL after 200 μg oral and vaginal administration, respectively.

The plasma AUC\text{inf} was lower in pregnant (326 pg·h/mL) vs. non-pregnant women (1009 pg·h/mL), but it should be noted when comparing the exposure that the duration of drug insertion was 24 h in non-pregnant and mean duration was 9 h (range 2-22 h) in pregnant women. The dose to non-pregnant women can approximately be calculated to (~80% released of 200 μg and molecular weight of the acid is 96.3% of parent) 154 μg and in pregnant women the median delivered dose was reported to be 66 μg (range 21-145 μg). Comparing the median total clearance (CL/F) it was 233 L/h and 153 L/h in pregnant and non-pregnant women, respectively, thus ca. 50% higher in pregnant women. The median plasma exposure (AUC\text{inf}) was 326 h·pg/mL (range 90-776) in pregnant women, thus in the same order as a single oral dose of 200 μg of Cytotec® in non-pregnant women (375 h·pg/mL). Cytotec® 200 μg can according to product label be dosed up to four times daily to patients as prophylaxis for gastric ulcers. Thus, the systemic exposure after a single vaginal 200 μg Misodel dose is low compared to the maximal recommended daily chronic dosing of oral Cytotec®. Also, since the administration of Misodel is based on effect i.e. the vaginal insert will be removed if labour commences or adverse effects occur, this in combination with the Misodel single dose use and the short half-life of misoprostol acid (40 min) it can be concluded that the risk of over-exposing subjects using the misoprostol vaginal insert (MVI) is low.
Figure 1. Mean Plasma Misoprostol Acid Concentrations in non-pregnant women

There is no study on milk excretion in humans of misoprostol acid after Misodel administration. However, in studies after oral dosing of 600 and 200 μg misoprostol acid has been detected in breast milk (Abdel-Aleem et al, Eur. J. Obster. Gynecol. 2003 and Vogel et al Am. J. Obster. Gynecol, 2004). In the publication by Abdel-Aleem et al the AUC(0-5h) was 290 and 51 pg-h/mL in plasma after postpartum and colostrum, respectively, i.e. nearly six times higher exposure in maternal plasma compared to colostrum. A negligible amount of misoprostol acid (<1 pg/mL) was detected in colostrum 5 h after oral intake. In the case of Misodel the MVI is removed when labour commences and the median half-life in plasma of misoprostol is 40 minutes after removal. After five half-lives i.e. approximately 3 h the levels in the maternal plasma is negligible. Misoprostol acid will most likely be excreted in colostrums/breast milk after Misodel administration, but exposure in neonates will be limited based on the knowledge of limited milk excretion after oral dosing and also taking into account the delay from removal of MVI and start of breast feeding the amount of misoprostol acid that could be ingested by the newborns is expected to be very low and should not be any hindrance for breastfeeding.

Misoprostol and its metabolites are mainly excreted in urine (73% of the radioactivity) and there is some uncertainty of the degree of involvement of liver metabolism. However, since the dosing is based on effect i.e. the MVI will be removed if labour commences or adverse effects occur, this in combination with single dose use and short plasma half-life (~40 min) it is considered that the risk in renally and hepatically impaired subjects is low.

The information on the PK interaction potential for misoprostol is limited. Given the rapid elimination half-life of misoprostol and the single dose administration, there is most likely a limited effect of misoprostol on the pharmacokinetics of other medicinal products for this indication. There is no information on the possible influence of other medicinal products on misoprostol and it cannot be excluded that other medicinal products may affect the elimination of misoprostol acid. Since the administration of Misodel is based on effect i.e. the vaginal insert will be removed if labour commences or adverse effects occur, this in combination with the Misodel single dose use and the short half-life of misoprostol acid it can be concluded that the risk of over-exposing subjects using the MVI is low. Also, the risk for underexposing subjects due to induction of metabolism of misoprostol acid is low based on the individual dosing regimen. Overall, the risk of PK interactions with Misodel is considered to be low.
IV.2 Pharmacodynamics

No specific drug interaction studies were conducted as part of the clinical development programme. Concurrent use of oxytocic drugs or other labour induction agents with Misodel is contraindicated due to the potential for additive uterotonic effects. Tachysystole onset after drug removal was similar for both Misodel and dinoprostone vaginal insert (DVI) treated. Tachysystole for those who after a thirty-minute waiting period had oxytocin was about the same in both groups. The potential for interaction with other uterotonic drugs seems low also considering the half-life for misoprostol.

IV.3 Clinical efficacy

A total of 3243 women were studied in the clinical development programme. Totally 2115 subjects were exposed to any dose reservoir of misoprostol vaginal insert (MVI) and a total of 874 pregnant women at or near term gestation received Misodel.

Phase II Controlled and uncontrolled clinical trials

In study Miso-Obs 204 with 373 included women, Misodel (MVI 200) demonstrated a higher proportion, not statistically significant, of vaginal deliveries at 24 hours compared to MVI 100 (76.00% vs. 63.75%, respectively, p=0.057).

Study Miso-Obs-002 was performed in Europe. All included women were parous and had a modified baseline BS ≤ 6. The difference in median time to vaginal delivery was 2.5 hours shorter for MVI 200 compared to MVI 100. The effect of dose on achievement of vaginal delivery at 12 hours was most marked in the subgroup of women with a baseline mean Bishop score (mBS) of 3 or less.

Study Miso-Obs-003 was a dose-escalation including only nulliparous women who had a modified baseline BS ≤ 6. The median time to vaginal delivery for MVI 300 (14.0 hours) vs MVI 100 (14.4 hours) was marginally shorter.

In Miso-Obs-002 and Miso-Obs-003, there appeared to be little advantage in terms of efficacy in increasing the MVI reservoir dose from 100 mcg to 200 mcg. These studies were however limited and selected and makes a less robust base for comparing dose reservoirs.

Main studies (Miso-Obs-303 and Miso-Obs-004)

Study Miso-Obs-303
Totally 1358 subjects (678 MVI 200, 680 DVI) were randomised in the study and all included women completed the study. The general demographic and baseline characteristics were similar in both treatment groups. Mean age was 26.0 years and 70.8% had a BMI > 30.0 kg/m². The majority of women were nulliparous (65.7%). Mean BS at baseline was 2.4 and 2.3 in MVI 200 and DVI respectively. Mean gestational age at study drug administration was 39 weeks and 4 days.

The most common reasons for induction were a post-term pregnancy (32.2%), hypertension (12.2%) and elective delivery (12.2%).

For each efficacy endpoint for which a significant difference was observed, a subgroup analysis was also performed for parity, race, BMI and age. The treatment group difference
was also significant for nulliparous (p<0.001) and parous women (p<0.001). Shorter time to vaginal delivery was also demonstrated for MVI 200 for race, BMI, maternal age and gestational age.

The pharmaco-economic assessment confirmed that the mean duration of labour and delivery was about 8 hours shorter for MVI 200 subjects compared with DVI subjects (p<0.001) and that a significantly lower dose and duration of pre-delivery oxytocin was administered (p<0.001).

The mean duration of maternal hospitalisation was only slightly shorter for MVI 200 subjects (4.1 days) vs for the DVI subjects (4.5 days) (p<0.001). No difference was observed for the neonates regarding the mean duration of hospitalisation (3.5 days).

Study Miso-Obs-004
In this study were 1308 subjects enrolled and 1307 analyzed. MVI 100: 428 analyzed (62.4% nulliparae and 37.6% parous women); MVI 50: 443 analyzed (61.9% nulliparae and 38.1% parous women); DVI: 436 analyzed (61.7% nulliparae and 38.1% parous women).

Women who required a Cesarean section or went home without delivering were censored from the primary efficacy parameter, time to vaginal delivery. Five subjects (1.2%), 11 subjects (2.5%) and 7 subjects (1.6%) in the MVI 100, MVI 50 and DVI groups, respectively, went home undelivered after this induction attempt.

Baseline demographics were similar across all groups for parity, baseline membrane status, gestational age, modified Bishop’s score and reasons for induction.

Post term was the most common reason for induction followed by elective induction, hypertension, oligohydramnios, diabetes and pre-eclampsia.

Comparison of Efficacy Results in the Phase III Studies
The Phase III studies (Miso-Obs-303 and Miso-Obs-004) were double-blind, randomised studies that had similar major entry criteria. Although different dose reservoirs of the MVI were used in these studies (MVI 200 in Miso-Obs-303 and MVI 50 and 100 in Miso-Obs-004), these studies used the same active comparator, DVI.

Comparison of efficacy results in these studies are given in the table below and indicates that MVI 200 had the shortest time (hours) to vaginal delivery and the highest rate of spontaneous vaginal delivery compared with groups treated with DVI, MVI 100 and MVI 50.
The integrated analyses of the Miso-Obs-004, Miso-Obs-204 and Miso-Obs-303 studies including around 3000 women, showed that time to vaginal delivery decreased with increasing dose reservoir and higher release rates of the MVI. Time to vaginal delivery during first hospitalisation was for MVI 200 subjects 21.3 hours compared with DVI subjects 30.5 hours, \( p<0.001 \).

The effect of parity, race, BMI, maternal age, and gestational age for time to vaginal delivery was also assessed. Shorter time to vaginal delivery was also demonstrated for MVI 200 for race, BMI, maternal age and gestational age. Subgroups of women who were induced for post-term >40 weeks but <41 weeks and women induced for post-term >41 weeks were analysed separately with regard to the co-primary endpoints in the integrated dataset from studies Miso-Obs-303, Miso-Obs-004, and Miso-Obs-204. The median time to delivery and rate of caesarean delivery were similar in both subgroups for both MVI 200 and DVI treatment groups.

### IV.4 Clinical safety

The total safety population included 2596 women. There were 809 women exposed to MVI 200 and 1116 women exposed to DVI. The safety documentation for Misodel (MVI 200) has been studied in 874 pregnant women at term gestation.

Induction of labour with prostaglandins is indicated in pregnant women in different circumstances including prolonged pregnancy, pre-existing hypertension, gestational hypertension, gestational diabetes mellitus (GDM), intra-uterine growth restriction (IUGR), non-reassuring stress test, premature rupture of membranes (PROM) and oligohydramnios. The compromising conditions present prior to the labour induction and events happening after removal of the insert but before delivery in a limited sample contribute to difficulties to assess the safety impact of MVI 200. Even in low-risk parous women elective induction of labour with cervical ripening means an increased risk of CS compared to spontaneous onset of labour (Jonsson M et al, Acta Obstet Gynecol Scand 2013).
Study Miso-Obs-303.
The primary safety objective was to assess the rate of cesarean delivery in subjects randomised to receive MVI 200 versus subjects randomised to receive DVI. Overall safety was also assessed by rate of adverse events during the intrapartum, postpartum, and neonatal periods.

Totally 1358 subjects (678 MVI 200, 680 DVI) were randomised in the study and included in the ITT population. All subjects in the ITT population completed the study. In each group there was a wide variation of the duration of the study drug in vagina reflecting differences in the obstetric characteristics at baseline (parity, BMI, gestational age, mBS) and differences related to labour and delivery.

Caesarean delivery
The rate of caesarean delivery during first hospitalization with MVI 200 (25.96%) was not shown to be non-inferior to the rate of caesarean delivery with DVI (27.06%). Similar to the overall rate were the results for the subgroup analyses for race, BMI, age and gestational age. Overall nulliparous women had higher rate of caesarean section compared to parous women.

Adverse events
Similar percentages of subjects in each treatment group had at least one intrapartum, postpartum or neonatal treatment-emergent AE, and at least one postpartum or neonatal treatment-emergent SAE.

Adverse events resulting in caesarean delivery that were not classified as serious adverse events included arrest of descent/failure to descend, arrest of dilatation/failure to dilate, fetal malpresentation, preeclampsia, chorioamnionitis, and hypertension.

The majority of subjects reported AEs that were at most mild or moderate severity, according to the Investigator, during the intrapartum, postpartum, and neonatal periods. There were no maternal, foetal or neonatal deaths in any of the studies in the clinical program.

A shorter time to active labour and vaginal delivery inevitably means increased uterine contractions and increased risk for AEs for the mother, the foetus and the neonate. Not unexpectedly, a higher rate of discontinuation of study drug was also observed in the MVI 200 group and at least one treatment-emergent intrapartum SAE (11.9% vs. 6.9%; p=0.002).

Shortening the duration of labour could among other things reduce maternal febrile morbidity (Gerli S et al. 2013, Grobman WA 2012). MVI 200 had decreased need for intrapartum and postpartum IV/IM antibiotics (Miso-Obs-303). These differences may reflect the longer durations of labour with DVI.

Reason for drug removal
In study Miso-Obs-303 there was a significant difference with shorter onset of active labour and with only 13% with drug in situ for 24 hours in the MVI 200 group vs 32% in the DVI group.

Intrapartum Adverse Events
A higher rate of abnormal labour affecting foetus was a treatment effect associated with MVI 200.

Postpartum Adverse Events
The most common treatment-emergent postpartum AE was postpartum haemorrhage, which occurred in 6.2% of subjects in the MVI 200 treatment group and 5.9% of subjects in the DVI treatment group.

Neonatal Adverse Events
Subjects with any treatment-emergent neonatal AEs were observed in 53.4% in the MVI 200 group vs 58.1% in the DVI group.

Serious Adverse Events
Only events that could have indicated fetal compromise or excess uterine activity resulting in cesarean delivery were reported as serious adverse events (e.g., category II or III FHR patterns, uterine tachysystole, uterine tachysystole with late decelerations, bradycardia, prolonged decelerations and cord compromise).

Intrapartum Serious Adverse Events
The only treatment-emergent intrapartum SAEs occurring in at least two subjects in either treatment group were foetal heart rate disorder (9.6% MVI 200, 6.8% DVI) and abnormal labour affecting foetus (1.9% MVI 200, 0% DVI).

A higher rate of FHR disorders and abnormal labour affecting the foetus in the MVI 200 group reflects the more uterotonic effect of this compound compared with the DVI treatment group.

Postpartum Serious Adverse Events
A similar rate of postpartum TEAs was observed in the mothers in the MVI 200 and DVI groups.

Neonatal Serious Adverse Events
Treatment-emergent neonatal SAEs occurring in ≥1.0% of subjects included atrial septal defect (1.2%) in the MVI 200 treatment group and pilonidal cyst congenital (1.0%) in the DVI treatment group. Two related neonatal SAEs occurred: foetal acidosis (one MVI 200 subject) and hypoxic-ischaemic encephalopathy (one MVI 200 subject).

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Two Serious Unexpected Suspected Adverse Drug Reactions were reported as Investigational New Drug safety reports during the study period (uterine rupture and neonatal hypoxic-ischaemic encephalopathy); both subjects were in the MVI 200 group. In both cases of SUSARs there were confounding factors and no causal safety signal was identified.

Outcomes and Adverse Events of Special Interest
Similar percentages of subjects in each treatment group had the most commonly occurring AE of category II FHR patterns; similar percentages were also noted for having had any category II/III FHR patterns.

No treatment group differences were noted for incidence of the majority of AEs and outcomes of special interest, including intrapartum resuscitations, instrumented vaginal delivery during first hospitalization, ICU/NICU admissions, postpartum haemorrhage, and neonatal respiratory events.
Uterine tachysystole was reported with the highest proportion in the MVI 200 groups. Increased risk of tachysystole is reported with different prostaglandins used for induction of labour (Vayssière C et al, 2013).

Safety Miso-Obs-004
Reasons for Cesarean section were similar across all three groups, with an adverse event as the leading cause in approximately 80% of Cesareans. The most common adverse events leading to a Cesarean section were non-reassuring FHR, dystocia and arrest of dilatation. Additional reasons for Cesarean section included failure to progress and failed induction.

The percentage of subjects who experienced adverse events was similar for the three treatment groups within each of the maternal/foetal, maternal post partum and neonatal categories.

There was one admission to ICU in the maternal/fetal category (DVI) and one in the maternal (post partum) group (MVI 50). Admissions to neonatal ICU were 6.8% in the MVI 100 group, 4.7% for MVI 50 and 7.6% for DVI.

Phase II Studies
Study Miso-Obs-204
The Overall frequencies of adverse events and Serious Adverse Events (SAEs) were similar across the three treatment groups MVI 100, MVI 150 and MVI 200. MVI 200 had the lowest rate of cesarean delivery during first hospitalization (22.9%) compared to MVI 100 and MVI 150 (31.4% and 30.4%, respectively).

Study Miso-Obs-002
The study compared different MVI doses in parous women. The most common adverse event reported overall was ‘Fetal Heart Rate Disorder Not Otherwise Specified (NOS)’. This was reported in 26 (21%) women and there was no obvious relationship to the dose of study drug. The serious adverse event (SAE) profile was similar across the four groups and all SAEs had resolved by the end of study. Vital signs data recorded throughout the study and physical examination of the neonate do not raise any issues regarding the safety of the study drug.

Study Miso-Obs-003 was a dose-escalation study in nulliparous women for calculation of the maximum tolerated dose in Part A and in Part B the relative efficacy of varying drug reservoir doses of the MVI was assessed. Adverse events noted in this study were, for the most part, those expected in a labour and delivery setting. There was evidence of increased numbers of adverse events in the 200 and 300 μg dose groups as compared to the lower dose groups; there is no discernible dose relationship in the occurrence of SAEs.

Outcomes and Adverse Events of Special Interest
Treatment-Emergent Adverse Events of Special Interest was studied in Miso-Obs-303. The MVI 200 treatment group had a higher percentage of subjects with any tachysystole. The greatest proportion of TEAs are related to related to uterine tachysystole in both treatment groups.

IV.5 Discussion on the clinical aspects

Aspects on clinical efficacy
Active management of labour is a multifaceted approach to shorten the duration of labour and to reduce maternal and foetal morbidity. Mode of delivery has been shown to be influenced by
parity, duration of labour (inversely proportional), maternal age (directly proportional) and cervical status, as classified by Bishop score (Gerli S et al. 2013, Grobman WA 2012).

The objectives, study design, endpoints and treatments and selection of study participants in the MVI programme seem representative and are acceptable. In the pivotal studies, the general demographic and baseline data were balanced and included women with cervical status of modified Bishop Score (mBS) ≤4 at baseline.

In Phase II Miso-Obs-002 and Miso-Obs-003, there appeared to be little advantage in terms of efficacy in increasing the MVI reservoir dose from 100 mcg to 200 mcg. These studies were however limited and selected and makes a less robust base for comparing dose reservoirs.

The Phase III studies indicate that MVI 200 had the shortest time (hours) to vaginal delivery and the highest rate of spontaneous vaginal delivery compared with groups treated with DVI, and lower MVI doses with less need of pre-delivery oxytocin in the MVI 200 group (48.1% vs 74.1%). The proportion with study drug in situ for 24 hours was 13.0% and 32.2 % for MVI 200 and DVI respectively.

The integrated analyses of the Miso-Obs-004, Miso-Obs-204 and Miso-Obs-303 studies including around 3000 women showed that time to vaginal delivery decreased with increasing dose reservoir and higher release rates of the MVI. Time to vaginal delivery during first hospitalisation was for MVI 200 subjects 21.3 hours compared with DVI subjects 30.5 hours, (p<0.001).

The mean duration of maternal hospitalisation was slightly shorter for MVI 200 subjects (4.1 days) vs for the DVI subjects (4.5 days) (p=0.001). No difference was observed for the neonates regarding the mean duration of hospitalisation.

In general, parous women have shorter time to vaginal delivery compared to nulliparous women. In the subgroup analysis, both nulliparous and parous women in the MVI 200 group had a significantly shorter median time to vaginal delivery compared with the DVI group (p<0.001). Overall, the subgroup analyses for race, BMI, and gestational age had similar results with shortest time to delivery in the MVI 200 group.

In conclusion, for the primary endpoint, the MVI 200 group demonstrated the shortest time to vaginal delivery in the MVI programme.

**Aspects on clinical safety**

Induction of labour with prostaglandins is indicated in pregnant women in different circumstances including prolonged pregnancy, pre-existing hypertension, gestational hypertension, gestational diabetes mellitus (GDM), intra-uterine growth restriction (IUGR), non-reassuring stress test, premature rupture of membranes (PROM) and oligohydramnios. The compromising conditions present prior to the labour induction and events happening after removal of the insert but before delivery in a limited sample contribute to difficulties to assess the safety impact of MVI 200. Even in low-risk parous women the electively induction of labour with cervical ripening means an increased risk of CS compared to spontaneous onset of labour (Jonsson M et al, Acta Obstet Gynecol Scand 2013).

Mode of delivery has been shown to be influenced by parity, duration of labor (inversely proportional), maternal age (directly proportional) and cervical status, as classified by Bishop score (Gerli S et al. 2013, Grobman WA 2012).
The contribution of labour induction to caesarean delivery among nulliparous women at term, with and without medical or obstetric complications, has been estimated to be approximately 20% (Ehrenthal DB et al, 2010). Overall, nulliparous women had higher rate of caesarean sections compared to parous women which is expected.

In Miso-Obs-303, the wide variation of the duration of the study drug in vagina in each group, probably reflects differences in the obstetric characteristics at baseline (parity, BMI, gestational age, mBS) and differences related to labour and delivery.

A shorter time to active labour and vaginal delivery inevitably means increased uterine contractions and increased risk for AEs for both the mother, the foetus and the neonate. Not unexpectedly a higher rate of discontinuation of study drug was also observed in the MVI 200 group and at least one treatment-emergent intrapartum SAE (11.9% vs. 6.9%; p=0.002).

For women with serious compromising conditions also arrest of descent/failure to descend or arrest of dilatation/failure to dilate can be considered to be a SAE. The potential for increased need of oxytocin among these women could also contribute to fetal morbidity (Jonsson M et al, Acta Obstet Gynecol Scand 2007, Jonsson M et al, BJOG 2009).

Treatment-emergent intrapartum AEs occurring in ≥10.0% of MVI 200 subjects were foetal heart rate disorders, meconium in amniotic fluid, arrested labour and abnormal labour affecting foetus. Treatment-emergent intrapartum AEs occurring in ≥10.0% of DVI subjects were foetal heart rate disorder, arrested labour, and meconium in amniotic fluid. A similar rate of postpartum TEAs was observed in the mothers in the MVI 200 and DVI groups.

No treatment group differences were noted for incidence of the majority of AEs and outcomes of special interest, including intrapartum resuscitations, instrumented vaginal delivery during first hospitalization, ICU/NICU admissions, postpartum haemorrhage, and neonatal respiratory events.

In study Miso-Obs-004 the percentage of subjects who experienced adverse events was similar for the three treatment groups within each of the maternal/foetal, maternal post partum and neonatal categories.

It is acknowledged that different doses of MVI imply different safety profiles. Induction of labour should only take place in a hospital setting by trained obstetric personnel where facilities for continous fetal and uterine monitoring is available which the SmPC states. The decision for induction of labour is also a question for careful health care professional consideration.

In the provided studies, the shorter duration of labour means no unexpected safety signal for the woman or the fetus/infant from MVI 200.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Overall conclusion

For the primary endpoint, the Misodel (MVI 200) group demonstrated the shortest time to vaginal delivery in the MVI programme. In the provided studies, the shorter duration of labour means no unexpected safety signal for the woman or the fetus/infant from MVI 200.
**Benefit**

The development of MVI 200 combines a consistent dose reservoir, in a single vaginal administration up to 24 hours, with a controlled release at a known rate, and it can be removed when the drug is no longer required.

Active management of labour is a multifaceted approach to shorten the duration of labour with the aim to reduce maternal and foetal morbidity. Mode of delivery has been shown to be influenced by parity, duration of labour (inversely proportional), maternal age (directly proportional), cervical status, as classified by Bishop score (Gerli S et al. 2013, Grobman WA 2012).

Induction of labour with prostaglandins is indicated in women with a low mBS (Gerli S et al. 2013). In general, labour induction contributes to caesarean delivery among nulliparous women at term, with and without medical or obstetric complications, the rate having been estimated to approximately 20% (Ehrenthal DB et al, 2010). In post-term pregnancies with unfavourable cervical status, prostaglandins can reduce recourse to oxytocin and diminish the doses needed (Vayssière C et al, 2013) which is an important benefit.

In Phase II Miso-Obs-002 only a 2.5 hour difference in labour time was observed between the 100 mcg MVI and 200 mcg MVI. In Miso-Obs-003, there was no dose-dependent effect on labour time between the 100 mcg, 200 mcg and 300 mcg MVI. Both studies were however limited and selected. Miso-Obs-002 included only parous women with a large proportion of post-term pregnancies whereas Miso-Obs-003 included only nulliparous women with a low proportion of post-term pregnancies. Cervical status as classified by mBS was in both studies $\leq 6$, which is higher than in the pivotal study Miso-Obs-303, and higher as compared with the what the company is applying for. Thus, these studies constitute a less robust basis for comparing dose reservoirs in the proposed target population.

Study Miso-Obs-204 provides a comparison between different MVI doses in a population of both parous and nulliparous (around 64%) women. In a sample of 373 subjects, of which 30 % were post-term, and with a mBS $\leq 4$, the proportion of subjects with vaginal delivery within 24 hours was highest in the MVI 200 group (76.0% % vs 63.8 % for the 100 mcg MVI).

The use of oxytocin intra-partum was reduced in the MVI 200 group (48.85%) as compared to the MVI 100 dose (70.94%) which is a clinical benefit.

Study Miso-Obs-004 (n=1307) compared lower doses of MVI with the 10 mg dinoprostone vaginal insert (DVI). The study did not demonstrate a reduction in the time to vaginal delivery with MVI 100 versus DVI (p=0.974) and the rates of Caesarean delivery were comparable.

The integrated analysis of the Miso-Obs-004, Miso-Obs-204 and Miso-Obs-303 studies showed that time to vaginal delivery decreased with increasing dose reservoir and higher release rates of the MVI. Time to vaginal delivery during first hospitalisation was for MVI 200 subjects 21.3 hours compared with DVI subjects 30.5 hours,(p<0.001). The corresponding time was for MVI 100 27.3 hours compared with the DVI group (p=0.580).

The difference in time to delivery with MVI-200 vs. lower dose reservoirs is considered clinically relevant.

In conclusion, for the primary endpoint, the MVI 200 group, compared to the DVI group, demonstrated a shortened duration of labour to vaginal delivery.
Risk
Induction of labour with prostaglandins is indicated in pregnant women in different circumstances including prolonged pregnancy, pre-existing hypertension, gestational hypertension, gestational diabetes mellitus (GDM), intra-uterine growth restriction (IUGR), nonreassuring stress test, premature rupture of membranes (PROM) and oligohydramnios. The compromising conditions present prior to the labour induction and events happening after removal of the insert but before delivery in a limited sample contribute to difficulties to assess the safety impact of MVI 200. Even in low-risk parous women the electively induction of labour with cervical ripening means an increased risk of CS compared to spontaneous onset of labour (Jonsson M et al, Acta Obstet Gynecol Scand 2013).

In study Miso-Obs-204, the important safety outcomes studied were Caesarean delivery, need for tocolysis and 5-minute Apgar score. The total number of CS was 105/374 with the lowest proportion of CS in MVI 200 groups (31.4% vs 22.9%, p=0.153) irrespective of parity (0.141). Breaking down the results further, 9.3% subjects had Caesarean delivery due to a non-reassuring FHR pattern adverse event in the MVI 100 group and 13.7% in the MVI 200 group.

The events relating to uterine hypertonus, uterine tachysystole (defined as >5 contractions in 10 min) and uterine hyperstimulation syndrome increased in relation to dose reservoirs of increasing strength. The need for tocolysis was however not proportionally increased, and the need compared to the rate of tachysystole was relatively lower in the MVI 200 group.

Increased risk of tachysystole is reported with different prostaglandins used for induction of labour (Vayssière C et al, 2013). A clinically important tachysystole is related to the presence of abnormal FHR tracings.

FHR tracings should be evaluated in the context of many maternal and foetal conditions. Category II FHR tracings are not predictive of abnormal foetal acid–base status but require evaluations. Category III tracings are predictive of abnormal foetal acid–base status at the time of observation. Category III FHR tracings require prompt evaluation such as discontinuation of labour stimulation (Macones GA et al, 2008).

During treatment there was, not unexpectedly, about twice as much tachysystole for MVI 200 compared to DVI (49.1% vs 24.6%, Miso-Obs-303). Tachysystole onset after drug removal was similar for both groups. Tachysystole for those who after removal of vaginal delivery system had oxytocin was about the same in both groups.

There were very few Category III events, but for those that did occur there was a similar pattern for these events as with the Category II events, with more events beginning after study drug had been discontinued (Miso-Obs-303).

The incidence of non-reassuring FHR pattern adverse events (mostly Category II) was not dose-related within the MVI group (Miso-Obs-204) and the lowest rate was reported for the MVI 200 (54.2%). The uneven use of oxytocin among the study groups might also contribute to these results (Jonsson M et al, Acta Obstet Gynecol Scand 2007).

There were no differences in mean or median Apgar scores at 1 minute or 5 minutes for the MVI groups. There were two neonates that had 5-minute Apgar scores <7, one each in the MVI 150 and MVI 200 treatment groups. Both of these neonates recovered without sequelae.

It is agreed with the applicant that there was an excess of certain events in the MVI 200 group that should not be attributed to study drug or with very low likelihood of being related, such as congenital anomalies and umbilical cord around the neck. However, such events could result
in non-reassuring FHR patterns. There was no apparent increased risk to the foetus or infant with MVI 200 compared with MVI 100, based on study Miso-Obs-204.

Uterine rupture and premature separation of the placenta are events that can be caused by compromising conditions present prior to the labour induction and excessive uterine contractility. From the available data it is not possible to determine if the incidence of uterine rupture or premature separation of the placenta is related to uterine hypertonus of the MVI 200 dose reservoir since only 2 events were reported (one of each type). There was also 1 case of premature separation of the placenta in the MVI 100 group.

Shortening of the duration of labour could among other things reduce maternal febrile morbidity (Gerli S et al. 2013, Grobman WA 2012). MVI 200 had decreased the need for intrapartum and postpartum IV/IM antibiotics (6.9% with MVI 200 vs 9.7 % DVI; Miso-Obs-303). These differences may reflect the longer duration of labour with DVI.

In the pivotal study Miso-Obs-303, there was a wide variation of the duration of the study drug in vagina in each group, probably reflecting differences in the obstetric characteristics at baseline, and that the dose reservoir was removed when it was no longer required. The highest rate of discontinuation of study drug was also observed in the MVI 200 group.

A shorter time to active labour and vaginal delivery inevitably means increased uterine contractions and increased risk for AEs for both for the mother, the foetus and the neonate. Not unexpectedly a higher rate of discontinuation of study drug was also observed in the MVI 200 group and at least one treatment-emergent intrapartum SAE (11.9% vs. 6.9%; p=0.002). The rate of CS in the MVI 200 group was however comparable to the DVI group.

For women with serious compromising conditions also arrest of descent/failure to descend or arrest of dilatation/failure to dilate can be considered to be a SAE. The potential for increased need of oxytocin among these women could also contribute to foetal morbidity (Jonsson M et al, Acta Obstet Gynecol Scand 2007, Jonsson M et al, BJOG 2009). The proportion of patients in need for oxytocin was lower for the MVI 200 group (48.1%) compared to the DVI group (74.1%).

In the provided studies, the shorter duration of labour means no unexpected safety signal for the woman or the foetus/infant from MVI 200.

**Benefit-risk balance**

Shortening the duration of labour reduces maternal and foetal morbidity in pregnant women with different compromising conditions present prior to the labour induction. Misodel permits induction in a controlled way and it can be removed when the drug is no longer required. The use of oxytocin intra-partum was reduced and the time to vaginal delivery was shortened in the Misodel group as compared to lower MVI doses and the DVI group which is a clinically important benefit.

A shorter time to active labour and vaginal delivery inevitably means increased uterine contractions and increased risk for AEs for both for the mother, the foetus and the neonate. The rate of CS in the Misodel group was however comparable to the DVI group.

The need for tocolysis was not proportionally increased, and the need compared to the rate of tachysystole was relatively lower in the Misodel group. Tachysystole onset after drug removal was similar for both groups. Tachysystole for those who after removal of vaginal delivery system had oxytocin was about the same in both Misodel and DVI groups respectively. The incidence of non-reassuring FHR pattern adverse events (mostly Category II) was not dose-related within the MVI group and the lowest rate was reported for Misodel.
For women with serious compromising conditions also arrest of descent/failure to descend or arrest of dilatation/failure to dilate can be considered to be a SAE. The potential for increased need of oxytocin among these women could also contribute to foetal morbidity. The lower need for oxytocin observed with Misodel 200 compared with DVI is considered of clinical relevance.

Shortening of the duration of labour could among other things reduce maternal febrile morbidity. Misodel had decreased the need for intrapartum and postpartum IV/IM antibiotics. These differences may reflect the longer duration of labour with DVI.

There were no differences in mean or median Apgar scores at 1 minute or 5 minutes for the MVI groups. No treatment group differences were noted for incidence of NICU admissions. Induction of labour should only take place in a hospital setting by trained obstetric personnel where facilities including continuous foetal and uterine monitoring are available - which the SmPC states. The decision for induction of labour is also a question for careful health care professional consideration and selection of the most appropriate case for induction with Misodel.

In conclusion:
The benefit risk for this product is considered positive.

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

The risk/benefit ratio is considered positive and Misodel, 200 micrograms, vaginal delivery system is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Misodel, 200 micrograms, vaginal delivery system was successfully finalised on 2013-10-16.
Public Assessment Report – Update

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<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
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