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(71) Applicant: **Ferring B.V.**
2132 JX Hoofddorp (NL)

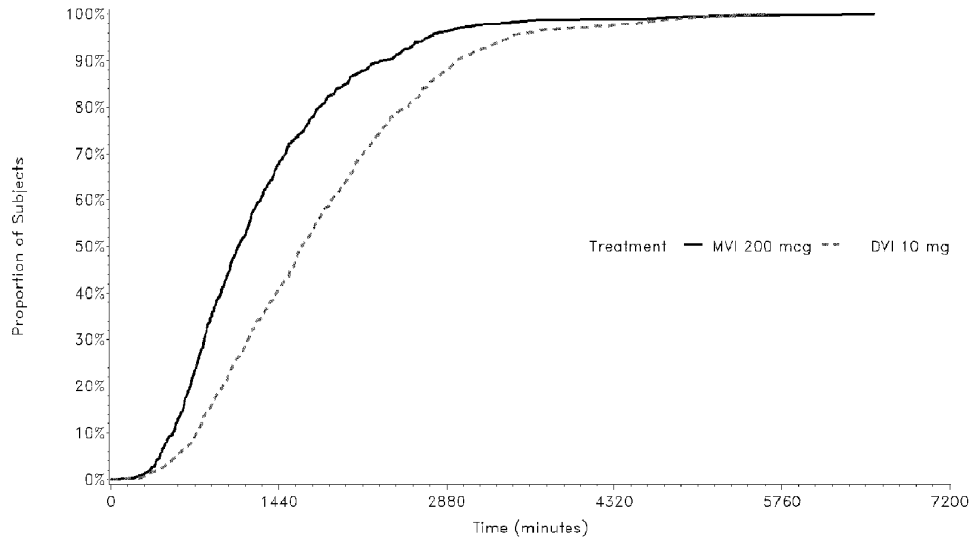
(72) Inventor: **The designation of the inventor has not yet been filed**

(74) Representative: **Gibbs, Richard**
Marks & Clerk LLP
Aurora
120 Bothwell Street
Glasgow G2 7JS (GB)

(54) Misoprostol for the induction of labour

(57) A method of reducing the likelihood of infection requiring use of antibiotics during or after induction of labour in a female, comprises administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol;
the likelihood of infection being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

Figure 1: Kaplan-Meier Plot of Time to Any Delivery (All Parity)



p = < 0.001 (Two-sided Log-Rank Test)

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Description

[0001] The present invention relates to the use of misoprostol for the induction of labour in a pregnant female, and in particular to the use of a sustained delivery device or insert containing substantially 200 μg misoprostol for intravaginal use. Such use includes methods of therapy and compositions for use in such methods.

[0002] Misoprostol is a synthetic analogue of prostaglandin E_1, and has been increasingly used for cervical ripening and labour induction administered both vaginally and orally. In some countries, it is available as a 100 μg or 200 μg tablet, which is quartered or halved and then placed in the vagina every four to six hours. However, splitting tablets does not provide adequate control of dosing of misoprostol, nor is drug release from the tablet fragments steady or well defined.

[0003] Our patent application WO2004/029125 discloses a controlled release vaginal pessary comprising misoprostol in a cross-linked polyurethane polymer. Sustained release data in vitro is provided. Our patent application WO2006/013335 discloses that the long term storage properties of such misoprostol cross-linked polyurethane sustained release devices may be improved by maintaining the water content at a low level.

[0004] A prostaglandin-containing vaginal pessary has been available for a number of years under the trade mark Propess/Cervidil. It contains 10mg of the PGE2 prostaglandin dinoprostone in a cross-linked polyurethane matrix for sustained vaginal release. The pessary is contained within a net bag and has a retrieval cord or tape, allowing the pessary to be withdrawn once the desired dose has been administered or when the woman reaches an appropriate stage during labour.

[0005] Cross-linked polyurethane formulations containing a prostaglandin are also disclosed in US4931288.

[0006] Patents US6642278, US2004/044080 and WO2003/011301 disclose other background information.

[0007] The normal gestation period in a human female is around 40 weeks. Induction of labour may be considered if the pregnancy progresses beyond the 40 week term without the baby being born. Generally, induction is considered if the pregnancy goes beyond the 41 st or 42nd week. Induction may also be considered for a variety of other medical reasons. The so called "Bishop Score" and "Modified Bishop Score" are pre-labour scoring systems used to assess the progression of labour and/or to determine whether induction of labour will be required. The duration of labour is inversely correlated with the Modified Bishop Score; a score that exceeds 8 describes a patient most likely to achieve a successful vaginal birth. Modified Bishop Scores of less than 4 usually require that a cervical ripening method be used before other methods. The determination of a Bishop score and/or Modified Bishop Score involve assessing certain factors including, cervical dilation, length of cervix, cervical effacement, cervical consistency, cervical position, and foetal station.

[0008] Induced labour tends to be more painful for the women and can lead to increased use of analgesics. It is also possible that induction may lead to an increased likelihood of caesarean section delivery for the baby. Medical reasons for the inducement of labour include hypertension or pre-eclampsia in the mother. However, induction may have adverse events, such as uterine tachysystole, foetal heart rate (FHR) irregularities, meconium in amniotic fluid, poor neonatal condition (Apgar score), postpartum haemorrhage, chorioamnionitis, diabetes and poor neonatal respiration.

[0009] Misoprostol controlled release pessaries have been investigated for possible clinical use and results are disclosed in a number of references including Powers et al. Journal of Clinical Pharmacology 2008, 48: 26-34, Ewert et al., Obstet Gynecol 2006; 108: 1130-7, Wing et al., J Reprod Med 2008; 53: 695-696, Castaneda et al. American Jn of Obstet Gyneco 2005; 193; 1071-5, Rayburn et al., J Soc Gynecol Investig 2006; 13: 112-7, Pevzner et al, Obstet Gynecol 2009; 114: 261-7, Wing Obster Gynecol 2008; 112: 801-12, Wing et al., Obstet Gynecol 2011; 117: 533-41, Pevzner et al., Obstet Gynecol 2009; 114, 1315-21 and Pevzner et al., European J Obstet Gynecol and Repr Biology 2011: 156, 144-148. Results of clinical trials are also disclosed in our publication WO2011/156812, where the principal basis of comparison is absence of drug or escalating misoprostol dosage. Generally speaking, these studies show improved speed to vaginal delivery using misoprostol 200 μg pessaries without increased rate of caesarean delivery.

[0010] The present application is based on the discovery of further surprising benefits of misoprostol - containing controlled release vaginal pessaries.

[0011] The present invention provides in one aspect a method of reducing the time from start of active labour to delivery after induction of labour in a female, which comprises administering intravaginally to the female an insert comprising a cross-linked reaction production of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol; the time being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

[0012] Another aspect provides a method of reducing the likelihood of infection requiring use of antibiotics during or after induction of labour in a female, which comprises administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol;

[0013] the likelihood of infection being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

[0014] Inserts containing 200μg misoprostol or 10 mg dinoprostone may also be referred to as containing a "dose reservoir". For example, inserts containing 200μg misoprostol may be said to comprise a "200μg (dose) reservoir of misoprostol". One of skill will appreciate that the phrase "dose reservoir" may be a reference to the total amount of a

therapeutic agent contained within any given delivery device - for example a vaginal insert. Once deployed within a patient, a device may release therapeutic agent from the reservoir. The release may be defined as a controlled release where, for example, predetermined quantities of agent are released from the device over a predetermined period of time or at predetermined intervals. The release may further be defined as a "sustained release" where release of the therapeutic agent in maintained (at a constant or variable rate) throughout the period of deployment.

[0015] A further aspect provides a method of reducing the time of drug dosing during induction of labour in a female, which comprising administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol; the time being reduced in comparison to the administration of said insert containing 10 mg disoprostone.

[0016] The invention also relates to the therapeutic use of the misoprostol-containing insert in any of these methods in a human female; or method of manufacture thereof; and to the use of the misoprostol-containing insert for the induction of labour in a female suffering from any of the clinical situations described herein (hypertension, preeclampsia, intrauterine growth restriction, membranes rupture etc.). Labour-associated adverse effects may be reduced.

[0017] The effect of the misoprostol-containing insert is compared to a dinoprostone-containing insert in the same cross-linked polyurethane. The term "insert" refers to the polyurethane hydrogel sustained delivery device, which may be loaded with drug (misoprostol; or dinoprostone for comparison). The term MVI 200 (or just MVI) refers to a formulated polyurethane insert containing 200 μg misoprostol. The term DVI refers to a formulated polyurethane insert containing 10 mg dinoprostone, which is used as the basis for comparison in the experimental data herein. The drug-containing insert may also be referred to as a pessary. In the experimental data herein the term "insert" is also used to include drug-loaded inserts.

[0018] The insert provides a sustained controlled delivery of misoprostol vaginally to the patient. Retrieval means may be provided for withdrawal of the drug-containing insert at a desired time according to clinical need.

[0019] The female may be parous or nulliparous.

[0020] Induction of labour may be needed in a number of clinical situations, including hypertension and pre-eclampsia. Induction is commonly due to the female being post-term (normally 40 weeks), for example in the range 40 to 41 weeks, or greater than or equal to 41 weeks. Induction may also be due to intrauterine growth restriction, or premature rupture of membranes.

[0021] Oxytocin may be provided to the female, especially for less than 8 hours during first hospitalisation.

[0022] A variety of infections may arise which require use of antibiotics, including chorioamnionitis. Such infections may be injurious to the mother or the baby (neonate). Infection may need to be treated intrapartum, post-partum or neonatally. Chorioamnionitis is caused by a (bacterial) infection and results in inflammation of the amnion and/or chorion (the foetal membranes). Chorioamniontis is known to prolong labour. The signs and/or symptoms of chorioamnionitis may include, for example, a fever (temperature > 37.5°C), uterine tenderness, purulent vaginal discharge and/or persistent maternal or fetal tachycardia. The antibiotic usage is the total antibiotics of all kinds administered to the female or neonate during such time period.

[0023] Delivery of the baby may be vaginally or by caesarean section. Vaginal delivery is either spontaneous or with instrumental assistance.

[0024] Misoprostol may act in cervical ripening and labour induction. It is surprising that duration of labour is reduced - even after the misoprostol-containing insert is removed from the female vagina.

[0025] Labour may be considered to comprise two phases. The first of these phases is known as the "latent" phase and the second is the "active phase". The latent phase of labour may be defined as beginning when regular uterine contractions commence and ends upon initiation of the active labour phase. Active labour may be defined as the phase in which progressive cervical dilatation to 4 cm with any frequency of contractions occurs or as the phase in which establishment of rhythmic, firm, adequate, quality uterine contractions at frequency of three or more in 10 minutes and lasting 45 seconds or more, is detected. These contractions may cause progressive cervical change. Accordingly, active labour may begin when the female reaches 4 cm of cervical dilation and the duration of active labour is typically expected to be 6 hours, during which time the cervix dilates further to 10 cm or becomes "fully dilated".

[0026] It has now been shown that the intravaginal administration of a misoprostol-containing insert reduces the duration of the latent and/or active phases of labour.

[0027] The misoprostol-containing insert is administered by introduction into the female at a time determined by the clinician. The time from administration to active labour (as defined herein) is referred to as the "time to active labour" and equates to the duration of latent labour. Once active labour is initiated, the time to delivery of the baby is referred to as "the time from active labour to delivery"; and this is the duration of active labour. The dosing period is the time from insertion of the drug-containing insert into the female to removal thereof.

[0028] Experimental clinical trial data will now be presented by way of example.

[0029] Figure 1 shows time to any delivery (including vaginal and cesarean delivery).

Experimental

Overall Study Design

[0030] This was a Phase III, double-blind, randomised, multicentre study of approximately 1,350 subjects at or near term gestation requiring cervical ripening and induction of labour.

[0031] Treatment consisted of administration of one randomly assigned MVI 200 or DVI. Nulliparous and parous subjects were randomised to their assigned treatments within their parity cohort in a double-blinded manner. The insert was to be kept in place for 24 hours unless events occurred that necessitated earlier removal (e.g., onset of active labour or intrapartum adverse event (AE)). Oxytocin was permitted after removal of the insert and completion of a 30-minute waiting period, if needed, to augment or induce labour. Enrollment was stratified by site and by parity, and randomization proceeded to ensure that approximately 60% nulliparous subjects and 40% parous subjects were enrolled.

Detailed Design

[0032] This Phase III study was a double-blind, randomised study comparing MVI 200 with DVI. DVI (Cervidil® [Forest Laboratories], Propess® [Ferring Pharmaceuticals]) is an appropriate comparator for MVI 200 because it is the most commonly used marketed cervical ripening product available in the US and because it is identical in appearance to the MVI, allowing the study to be double-blinded. DVI is labeled in the US for a single administration of a single dose with removal at 12 hours. However, there is an adequate amount of drug in the reservoir to allow continuous dosing via controlled release for up to 24 hours. Because of this, the product is approved in some European countries for administration up to 24 hours. The FDA agreed to allow dosing of up to 24 hours for the DVI during this study in order to maintain the blinded nature of the study.

[0033] The study was randomised in order to prevent bias in the administration of different treatment groups and to attempt to have an even distribution of baseline characteristics across the arms of the study.

[0034] Eligible subjects were randomised to receive one of the following treatments: MVI 200 or DVI

[0035] Subjects were treated with one vaginal insert for up to 24 hours, one time only. Intravenous oxytocin was permitted, when required, at least 30 minutes following removal of the study drug assuming no contraindications and active labour not present.

[0036] The MVI 200 and the DVI (Cervidil) were manufactured and released by Controlled Therapeutics (Scotland) Ltd.

[0037] The MVI had three components:

- a hydrogel polymer base measuring approximately 30 x 10 x 0.8 mm
- 200 mcg reservoir of misoprostol released at a controlled rate
- a retrieval tape consisting of inert woven polyester into which the polymer base was placed

[0038] The DVI had three components:

- a hydrogel polymer base measuring approximately 30 x 10 x 0.8 mm
- 10 mg reservoir of dinoprostone released at approximately 0.3 mg/hour
- a retrieval tape consisting of inert woven polyester into which the polymer base was placed.

[0039] Batch number information is provided in Table 1.

Table 1: Investigational Drug (MVI and DVI) Batch Numbers

Investigational Drug/Dose	Batch No.	Expiry Date
MVI 200 mcg	MS10006	31 July 2013
DVI 10 mg (Cervidil)	MA10K02/1	30 June 2013

[0040] For both the MVI and DVI, the polymer base was designed to absorb fluid from the vagina. As the polymer hydrates and swells, it creates a concentration gradient leading to a sustained release of misoprostol or dinoprostone for up to 24 hours. The polymer was a cross-linked polyurethane.

[0041] The MVI and DVI study drug inserts and packaging were identical in appearance (double-blinded). Each study drug kit consisted of a foil sachet with a preprinted subject number detailed on the label. The subject number differentiated study drug intended for nulliparous subjects from that intended for parous subjects. A second self-adhesive label identical to that found on the study drug foil sachet was attached to the study drug foil label. The second self-adhesive label was

placed on the study drug accountability form for that subject and kept with the study source documents.

[0042] The study drug kits were stored in a freezer. If unopened study drug was not used following removal from the freezer, it could have been returned to the freezer for use at a later date. The study drug could have been removed from and returned to the freezer multiple times as long as it was unopened and the total cumulative time outside the freezer was not more than 24 hours. Any study drug remaining out of the freezer for more than a total of 24 hours was discarded and its destruction documented.

Selection and Timing of Dose for Each Patient

[0043] Subjects were randomised to receive one of the following in a double-blind manner: MVI 200 or DVI.

[0044] One randomised study drug was administered to each subject by the Investigator or qualified designee. The insert was placed high in the posterior vaginal fornix and positioned transversely. A minimal quantity of water-soluble lubricant could have been used to aid placement of the study drug. The insert was not pre-wetted or pre-swelled prior to insertion and obstetric cream was not used.

[0045] The subject remained in bed for at least 30 minutes after insertion to ensure that sufficient time was provided for the insert to hydrate and start to swell.

[0046] The subject was instructed to use caution when using the toilet or washing to avoid inadvertent removal of the insert.

[0047] Subjects were treated with study drug for up to 24 hours. The study drug was removed before 24 hours if there was clinical concern for the wellbeing of mother or baby or if an adverse event (AE) occurred:

[0048] If the study drug fell out of the vagina spontaneously or was mistakenly removed early, it was not replaced. At the time of removal, an obstetrician, midwife, obstetric nurse, or other qualified site staff removed the insert by gently pulling on the retrieval tape.

Oxytocin Use

[0049] Oxytocin use was not permitted within 7 days prior to study drug administration and while the study drug was *in situ.*

[0050] Intravenous oxytocin was permitted, when required, at least 30 minutes following removal of the study drug, assuming no contraindications and no active labour. Earlier administration was permitted, if required, for treatment of an emergency situation.

Onset of Active Labour and Delivery

[0051] The date and time of onset of active labour were to be recorded throughout the treatment period. Active labour was defined as progressive cervical dilatation to 4 cm with any frequency of contractions OR rhythmic, firm, adequate, quality uterine contractions causing progressive cervical change occurring at a frequency of three or more in 10 minutes and lasting 45 seconds or more.

[0052] At time of delivery of neonate, the following were recorded:

- Mode of delivery (spontaneous vaginal, instrumented vaginal, or cesarean)
  - If caesarean delivery, the reason for the caesarean delivery was recorded.
- Date and time of delivery of neonate.

Adverse Events (AE)

[0053] An AE was defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

[0054] Subjects were questioned and observed for evidence of AEs, whether or not related to study drug.

[0055] Adverse events were collected through hospital discharge following delivery. Adverse events that occurred during the Labour and delivery (L&D) period were categorised as intrapartum AEs. Following delivery, AEs were categorised as postpartum (maternal) or neonatal events.

Summaries of Adverse Event Incidence Rates

[0056] Averse events were summarised by system organ class and preferred term for intrapartum, postpartum, and

neonate events without regard to relationship to study drug.

Summary of Outcomes and Adverse Events of Special Interest

[0057] Safety assessments were also summarised for Outcomes and AEs of Special Interest. Treatment groups were compared using Fisher's exact tests for each of these outcomes or events. However, there was no correction for multiplicity; therefore, p-values should be interpreted with caution.

Results

Time to Any Delivery (Vaginal or Caesarean) During the First Hospitalisation

[0058] Time to any delivery mode (vaginal or caesarean) was significantly shorter in MVI 200 subjects (Kaplan Meier median 1096.50 minutes [18.3 hours]) compared with DVI subjects (Kaplan Meier median 1639.50 minutes [27.3 hours]) ($p<0.001$). Time to any delivery was also significantly shorter in MVI 200 subjects compared with DVI subjects among both nulliparous subjects ($p<0.001$) and parous subjects ($p<0.001$). Kaplan Meier estimates of time to any delivery are presented Table 2.

[0059] Figure 1 shows time to any delivery for MVI200 versus DVI.

Table 2: Kaplan-Meier Estimates of Time to Any Delivery

Time From Study Drug Administration to Any Delivery (minutes)		MVI 200 (N=678)	DVI (N=680)
Any parity			
	N	678	680
	Median	1096.50	1639.50
	95% CI[1]	(1031.00, 1170.00)	(1573.00, 1731.00)
	p-value[1]	<0.001	
	Number (%) of censored subjects[2]	5 (0.7)	9 (1.3)
	Discharged prior to delivery (imputed value: 4571 minutes)	5 (0.7)	9 (1.3)
Nulliparous subjects			
	N	441	451
	Median	1304.00	1882.00
	95% CI[1]	(1203.00, 1376.00)	(1764.00, 2016.00)
	p-value[1]	<0.001	
	Number (%) of censored subjects[2]	4 (0.9)	8 (1.8)
	Discharged prior to delivery (imputed value: 4571 minutes)	4 (0.9)	8 (1.8)
Parous subjects			
	N	237	229
	Median	777.00	1155.00
	95% CI[1]	(732.00, 823.00)	(1040.00, 1321.00)
	p-value[1]	<0.001	
	Number (%) of censored subjects[2]	1 (0.4)	1 (0.4)
	Discharged prior to delivery (imputed value: 1642minutes)	1 (0.4)	1 (0.4)

[1] Two-sided p-values and CIs were obtained from a Log-Rank Test.

[2] Subjects who did not deliver during their first hospitalisation were censored using the longest time interval from study drug administration to L&D discharge, independent of treatment group.

[0060] The Kaplan-Meier plot of time to any delivery during the first hospitalisation is presented in Figure 1 (all parity).

Time to Active Labour (or duration of latent labour) During the First Hospitalisation

[0061] Active labour was defined as progressive cervical dilatation to 4 cm with any frequency of contractions OR rhythmic, firm, adequate, quality uterine contractions causing progressive cervical change occurring at a frequency of three or more in 10 minutes and lasting 45 seconds or more.

[0062] Time to active labour was significantly shorter in MVI 200 subjects (median 726.50 minutes [12.1 hours]) compared to DVI subjects (median 1116.50 minutes [18.6 hours]) ($p<0.001$). Time to active labour was also significantly shorter in MVI 200 subjects compared with DVI subjects among both nulliparous subjects ($p<0.001$) and parous subjects ($p<0.001$). Kaplan-Meier estimates of time to active labour are presented in Table 3.

Table 3: Kaplan-Meier Estimates of Time to Active Labour

Time From Study Drug Administration to Active Labour (minutes)	MVI 200 (N=678)	DVI (N=680)
Any parity		
N	678	680
Median	726.50	1116.50
95% CI[1]	(719.00, 773.00)	(1083.00, 1352.00)
p-value[1]	<0.001	
Number (%) of censored subjects[2]	47 (6.9)	54 (7.9)
Discharged without active labour (imputed value: 5618 minutes)	42 (6.2)	45 (6.6)
Discharged prior to active labour (imputed value: 4571 minutes)	5 (0.7)	9 (1.3)
Nulliparous subjects		
N	441	451
Median	885.00	1444.00
95% CI[1]	(810.00, 948.00)	(1352.00, 1558.00)
p-value[1]	<0.001	
Number (%) of censored subjects[2]	41 (9.3)	50(11.1)
Discharged without active labour (imputed value: 5618 minutes)	37 (8.4)	42 (9.3)
Discharged prior to active labour (imputed value: 4571 minutes)	4 (0.9)	8 (1.8)
Parous subjects		
N	237	229
Median	579.00	780.00
95% CI[1]	(535.00, 616.00)	(715.00, 913.00)
p-value[1]	<0.001	
Number (%) of censored subjects[2]	6 (2.5)	4 (1.7)
Discharged without active labour (imputed value: 1451 minutes)	5 (2.1)	3 (1.3)
Discharged prior to active labour (imputed value: 1642 minutes)	1 (0.4)	1 (0.4)

[1] Two-sided p-values and CIs were obtained from a Log-Rank Test.

[2] Subjects who did not go into active labour during the first hospitalisation were censored using the longest time interval from study drug administration to delivery during the first hospitalisation, independent of treatment group. Subjects who, in their first hospitalisation, were discharged prior to delivery or withdrew consent prior to delivery were censored using the longest time interval from study drug administration to L&D discharge, independent of treatment group.

Incidence of Cervical Ripening Success at 12 Hours

[0063] A higher percentage of subjects in the MVI 200 treatment group achieved the composite endpoint for cervical ripening at 12 hours than in the DVI treatment group (83.6%[a] vs. 67.5%[a], $p<0.001$[a] and 81.3%* vs 66.0%* $p<0.001$*: Table 4). The treatment group difference was also statistically significant among both nulliparous subjects ($p<0.001$) and parous subjects ($p<0.001$). Note: * denotes data from revised analysis of raw data used to generate the preliminary data ([a]).

Table 4: Composite Endpoint for Cervical Ripening at 12 Hours

	MVI 200 (N=678)[a]	MVI 200 (N-678)*	**DVI (N=680)[a]**	**DVI** (N=680)*
Any parity	678	678	680	680
Achieved composite endpoint for cervical ripening, n (%)[1]	567 (83.6)	551 (81.3)	459 (67.5)	449 (66.0)
95% CI[2]	(80.62%, 86.34%)	78.12%, 84.14%)	(63.84%, 71.01%)	(62.33%, 69.59%)
p-value[3]	<0.001	<0.001		
Nulliparous	441	441	451	451
Achieved composite endpoint for cervical ripening, n (%)	359 (81.4)	345 (78.2)	295 (65.4)	289 (64.1)
95% CI[2]	(77.45%, 84.93%)	74.08%, 82.00%)	(60.82%, 69.80%)	(59.46%, 68.51%)
p-value[3]	<0.001	<0.001		
Parous	237	237	229	229
Achieved composite endpoint for cervical ripening, n (%)[1]	208 (87.8)	206(86.9)	164 (71.6)	160 (69.9)
95% CI[2]	(82.90%, 91.65%)	81.95%, 90.94%)	(65.30%, 77.36%)	63.48%, 75.74%
p-value[3]	<0.001	<0.001		

[1] Achieved one or more of the following by 12 hours of treatment: increase from baseline in mBS ≥3, achievement of mBS ≥6, or vaginal delivery. If the subject had a caesarean delivery prior to hour 12, or if the subject had not delivered by hour 12 and the score was missing, the hour 6 Bishop score was used (LOCF).
[2] 95% exact binomial CI.
[3] Two-sided p-values were obtained from Fisher's exact tests.
[a] Preliminary data
* Data from revised analysis of raw data used to generate the preliminary data ([a]).

Time from Active Labour to Any Delivery

[0064] Time from onset of active labour to delivery (the duration of labour or active labour) is given in Tables 5.1 to 5.3 for any delivery, vaginal delivery and caesarean delivery.

Table 5.1

Time from Active Labour to Any Delivery During First Hospitalisation				
		MVI 100 (N=678)	**DVI (N=680)**	**Total (N=1358)**
Subjects with No Time to Active Labour	No Delivery During First Hospitalisation	5	9	14
	Delivery but No Active Labour	42	45	87
Time from Active Labour to Delivery During First Hospitalisation (min)	N	631	626	1257
	Mean	380.8	487.1	433.8
	SD	354.42	365.83	363.91
	Median	285.0	414.5	347.0
	Min, Max	0,3266	0,3309	0,3309

Table 5.2

Time from Active Labour to Vaginal Delivery During First Hospitalisation				
		MVI 100 (N=678)	DVI (N=680)	Total (N=1358)
Subjects with No Time to Active Labour	No Vaginal Delivery During First Hospitalisation	181	193	374
Time from Active Labour to Vaginal Delivery During First Hospitalisation (min)	N	497	487	984
	Mean	326.1	432.3	378.6
	SD	273.51	306.94	295.20
	Median	257.0	378.0	316.0
	Min, Max	0, 1874	0,2266	0,2266

Table 5.3

Time from Active Labour to Caesarean Delivery During First Hospitalisation				
		MVI 100 (N=678)	DVI (N=680)	Total (N=1358)
Subjects with No Time to Active Labour	No Caesarean Delivery During First Hospitalisation	502	496	998
	Caesarean Delivery but No Active Labour	42	45	87
Time from Active Labour to Caesarean Delivery During First Hospitalisation (min)	N	134	139	273
	Mean	583.8	679.4	632.5
	SD	513.16	475.88	495.93
	Median	460.5	585.0	545.0
	Min, Max	13,3266	0,3309	0,3309

Incidence of Subject/Neonate Antibiotic Use During First Hospitalisation

[0065] Overall, systemic antibiotic use was lower in the MVI 200 treatment group compared with the DVI treatment group.

[0066] The percentage of subjects who received intrapartum concomitant antibiotics (e.g., antibacterials for systemic use) was 8.1 %[a]/5.6%* in the MVI 200 treatment group and 11.3%[a]/8.7%* in the DVI treatment group. Intrapartum concomitant antibiotics received by ≥1.0% of subjects overall included ampicillin (4.0% MVI 200, 6.2% DVI), gentamicin (3.7%[a]/4.0%* MVI 200, 6.2% DVI), clindamycin (1.0% MVI 200, 1.9% DVI), and nitrofurantoin (1.2% MVI 200, 1.0% DVI).

[0067] The percentage of subjects who received postpartum concomitant antibiotics (e.g., antibacterials for systemic use) was 5.6%[a]/4.6%* in the MVI 200 treatment group and 9.6%[a]/8.4%* in the DVI treatment group. Postpartum concomitant antibiotics received by ≥1.0% of subjects overall included gentamicin (3.7% MVI 200, 5.9% DVI), ampicillin (2.7% MVI 200, 5.0% DVI), and clindamycin (2.5% MVI 200, 3.8% DVI).

[0068] The percentage of subjects who received neonate concomitant antibiotics (e.g., antibacterials for systemic use) was 7.2%[a]/6.9%* in the MVI 200 treatment group and 9.7% in the DVI treatment group. Neonate concomitant antibiotics received by ≥1.0% of subjects overall included ampicillin (7.1% MVI 200, 9.4% DVI) and gentamicin (6.5%[a]/6.8%* MVI 200, 9.0%[a]/9.3%* DVI).

[0069] Evidence of reduced total antibiotic use in various scenarios is provided in the following Tables. The scenarios are in respect of parous or nulliparous females, induction for hypertension, pre-eclampsia, post-term (40 - 41 weeks, greater than or equal to 41 weeks), intrauterine growth restriction, premature rupture of membranes, oxytocin use, and vaginal or caesarean delivery.

[0070] Note: * denotes data from revised analysis of raw data used to generate the preliminary data ([a]).

Table 6 (Reduced Antibiotics Usage)

Nulliparous Subjects			
	MVI 200 (N=441)	**DVI (N=451)**	**Total (N=892)**
Neonatal IV/IM Antibiotic Use	39 (8.8%)	55 (12.2%)	94 (10.5%
Intrapartum IV/IM Antibiotic Use	35 (7.9%)	53 (11.8%)	88 (9.9%)
Postpartum IV/IM Antibiotic Use	29 (6.6%)	48 (10.6%)	77 (8.6%)
Chorioamnionitis	34 (7.7%)	53 (11.8%)	87 (9.8%)

Table 7 (Reduced Antibiotics Usage)

Parous Subjects			
	MVI 200 (N=237)	**DVI (N=229)**	**Total (N=466)**
Neonatal IV/IM Antibiotic Use	8 (3.4%)	11 (4.8%)	19 (4.1%)
Intrapartum IV/IM Antibiotic Use	3 (1.3%)	6 (2.6%)	9 (1.9%)
Postpartum IV/IM Antibiotic Use	2 (0.8%)	9 (3.9%)	11 (2.4%)
Chorioamnionitis	4 (1.7%)	6 (2.6%)	10 (2.1%)

Table 8 (Reduced Antibiotics Usage)

Subjects Induced for Hypertension			
	MVI 200 (N=79)	**DVI (N=86)**	**Total (N=165)**
Neonatal IV/IM Antibiotic Use	3 (3.8%)	9 (10.5%)	12 (7.3%)
Intrapartum IV/IM Antibiotic Use	3 (3.8%)	9 (10.5%)	12 (7.3%)
Postpartum IV/IM Antibiotic Use	2 (2.5%)	10 (11.6%)	12 (7.3%)
Chorioamnionitis	1 (1.3%)	8 (9.3%)	9 (5.5%)

Table 9 (Reduced Antibiotics Usage)

Subjects Induced for Pre-eclampsia			
	MVI 200 (N=71)	**DVI (N=59)**	**Total (N=130)**
Neonatal IV/IM Antibiotic Use	4 (5.6%)	4 (6.8%)	8 (6.2%)
Intrapartum IV/IM Antibiotic Use	4 (5.6%)	5 (8.5%)	9 (6.9%)
Postpartum IV/IM Antibiotic Use	7 (9.9%)	4 (6.8%)	11 (8.5%)
Chorioamnionitis	4 (5.6%)	4 (6.8%)	8 (6.2%)

Table 10.1 (Reduced Antibiotics Usage)

Subjects Induced for Post Term			
	MVI 200 (N=210)	DVI (N=227)	Total (N=437)
Neonatal IV/IM Antibiotic Use	15(7.1%)	32(14.1%)	47 (10.8%)
Intrapartum IV/IM Antibiotic Use	14 (6.7%)	26 (11.5%)	40 (9.2%)
Postpartum IV/IM Antibiotic Use	11 (5.2%)	28 (12.3%)	39 (8.9%)
Chorioamnionitis	17 (8.1 %)	32 (14.1 %)	49 (11.2%)

Table10.2 (Reduced Antibiotics Usage)

Subjects Induced for Post-Term (40 - 41 weeks)			
	MVI 200 (N=91)	DVI (N=115)	Total (N=206)
Neonatal IV/IM Antibiotic Use	7 (7.7%)	17 (14.8%)	24 (11.7%)
Intrapartum IV/IM Antibiotic Use	8 (8.8%)	12 (10.4%)	20 (9.7%)
Postpartum IV/IM Antibiotic Use	7 (7.7%)	11 (9.6%)	18 (8.7%)
Chorioamnionitis	10 (11.0%)	15 (13.0%)	25(12.1%)

Table 10.3 (Reduced Antibiotics Usage)

Subjects Induced for Post Term (>= 41 weeks)			
	MVI 200 (N=119)	DVI (N=112)	Total (N=231)
Neonatal IV/IM Antibiotic Use	8 (6.7%)	15 (13.4%)	23 (10.0%)
Intrapartum IV/IM Antibiotic Use	6 (5.0%)	14 (12.5%)	20 (8.7%)
Postpartum IV/IM Antibiotic Use	4 (3.4%)	17 (15.2%)	21 (9.1 %)
Chorioamnionitis	7 (5.9%)	17 (15.2%)	24 (10.4%)

Table 11 (Reduced Antibiotics Usage)

Subjects Induced for Intrauterine Growth Restriction			
	MVI 200 (N=35)	DVI (N=35)	Total (N=70)
Neonatal IV/IM Antibiotic Use	0 (0.0%)	3 (8.6%)	3 (4.3%)
Intrapartum IV/IM Antibiotic Use	1 (2.9%)	3 (8.6%)	4 (5.7%)
Postpartum IV/IM Antibiotic Use	0 (0.0%)	1 (2.9%)	1 (1.4%)
Chorioamnionitis	1 (2.9%)	1 (2.9%)	2 (2.9%)

Table 12 (Reduced Antibiotics Usage)

Subjects Induced for Premature Rupture of Membranes			
	MVI 200 (N=22)	DVI (N=25)	Total (N=47)
Neonatal IV/IM Antibiotic Use	3 (13.6%)	5 (20.0%)	8 (17.0%)
Intrapartum IV/IM Antibiotic Use	3 (13.6%)	4 (16.0%)	7 (14.9%)
Postpartum IV/IM Antibiotic Use	2 (9.1 %)	4 (16.0%)	6 (12.8%)

(continued)

Subjects Induced for Premature Rupture of Membranes			
	MVI 200 (N=22)	DVI (N=25)	Total (N=47)
Chorioamnionitis	2 (9.1 %)	4 (16.0%)	6 (12.8%)

Table 13.1 (Reduced Antibiotics Usage)

Subjects with Oxytocin Duration <8 Hours in First Hospitalisation)			
	MVI 200 (N=189)	DVI (N=218)	Total (N=407)
Neonatal IV/IM Antibiotic Use	12 (6.3%)	16 (7.3%)	28 (6.9%)
Intrapartum IV/IM Antibiotic Use	7 (3.7%)	14 (6.4%)	21 (5.2%)
Postpartum IV/IM Antibiotic Use	7 (3.7%)	17 (7.8%)	24 (5.9%)
Chorioamnionitis	10 (5.3%)	13 (6.0%)	23 (5.7%)

Table 13.2 (Reduced Antibiotics Usage)

Subjects with Oxytocin Duration >=8 Hours in First Hospitalisation)			
	MVI 200 (N=132)	DVI (N=279)	Total (N=411)
Neonatal IV/IM Antibiotic Use	26 (19.7%)	43 (15.4%)	69 (16.8%)
Intrapartum IV/IM Antibiotic Use	21 (15.9)	39 (14.0%)	60 (14.6%)
Postpartum IV/IM Antibiotic Use	16 (12.1 %)	34 (12.2%)	50 (12.2%)
Chorioamnionitis	22 (16.7%)	41 (14.7%)	63 (15.3%)

Table 14.1 (Reduced Antibiotics Usage)

Subjects with Vaginal Delivery During First Hospitalisation)			
	MVI 200 (N=497)	DVI (N=487)	Total (N=984)
Neonatal IV/IM Antibiotic Use	23 (4.6%)	38 (7.8%)	61 (6.2%)
Intrapartum IV/IM Antibiotic Use	19 (3.8%)	27 (5.5%)	46 (4.7%)
Postpartum IV/IM Antibiotic Use	10 (2.0%)	27 (5.5%), 24 (4.9%)*	45 (4.6%), 34 (3.5%)*
Chorioamnionitis	18 (3.6%)	27 (5.5%)	45 (4.6%)
* Obtained by analysis of revised data.			

Table 14.2 (Reduced Antibiotics Usage)

Subjects with Caesarean Delivery During First Hospitalisation)			
	MVI 200 (N=176)	DVI (N=184)	Total (N=360)
Neonatal IV/IM Antibiotic Use	24 (13.6%)	28 (15.2%)	52 (14.4%)
Intrapartum IV/IM Antibiotic Use	19 (10.8%)	32 (17.4%)	51 (14.2%)
Postpartum IV/IM Antibiotic Use	21 (11.9%)	32 (17.4%)	53 (14.7)
Chorioamnionitis	20 (11.4%)	31 (16.8%)	51 (14.2%)

Extent of Exposure

[0071] The MVI is designed to be removed upon the occurrence of various clinical events (e.g., upon onset of active labour). Thus, variation in the duration of exposure (vaginal insert *in situ)* was expected, as each subject had study drug removed when exogenous prostaglandin was no longer desirable. Discontinuation of study drug prior to 24 hours was more often due to an efficacy reason such as onset of active labour (43.8% MVI 200, 34.1% DVI) than an AE (11.4% MVI 200, 4.0% DVI). Of note, the percentage of subjects with study drug *in situ* for >20 hours was 16.3% (16.4% by revised analysis of raw data) in the MVI 200 treatment group and 41.1% in the DVI treatment group.

[0072] Time of study drug *in situ* was statistically significantly shorter in the MVI 200 treatment group than in the DVI treatment group (mean: 712.6 minutes [11.9 hours] vs. 983.0 minutes [16.4 hours]). Duration of study drug *in situ* is summarised in Table 15.

Table 15: Duration of Study Drug *In situ*

	MVI 200 (N=678)	DVI (N=680)	p-value[1]
Duration of study drug *in situ* (minutes)			<0.001
N	673	676	
Mean (SD)	712.6 (391.52)	983.0 (435.84)	
Median	616.0	1034.5	
Minimum, maximum	60, 1508	48, 1560	
Exposure interval, n (%)			
≤240 minutes (≤4 hours)	38 (5.6)	28 (4.1)	
>240 to 480 minutes (>4 to 8 hours)	193 (28.7)	79 (11.7)	
>480 to 720 minutes (>8 to 12 hours)	182 (27.0)	116 (17.2)	
>720 to 960 minutes (>12 to 16 hours)	96 (14.3)	94 (13.9)	
>960 to 1200 minutes (>16 to 20 hours)	54 (8.0)	81 (12.0)	
>1200 to 1440 minutes (>20 to 24 hours)	51 (7.6)	125 (18.5)	
>1440 minutes (>24 hours)	59 (8.8)	153 (22.6)	

[1] Two-sided p-value was obtained from a one-way ANOVA model.

Outcomes and Treatment-Emergent Adverse Events of Special Interest

[0073] For ease of review, a summary of outcomes and AEs of interest in this obstetric setting across the three AE reporting periods of intrapartum, postpartum, and neonatal is provided in Table 16. This table also includes events that are not AEs but provide important safety information, such as Apgar scores, rate of caesarean delivery, intensive care unit (ICU) admission, and antibiotic use.

Table 16: Summary of Outcomes and Treatment-Emergent Adverse Events of special Interest

	Number (%) of Subjects			
	MVI 200 (N=678)[a]	DVI (N=680)[a]	p-value[1(a)]	p-value*
Uterine tachysystole (AE)	90 (13.3)	27 (4.0)	<0.001	
Requiring treatment (without FHR involvement)	25 (3.7)	9 (1.3)		0.005*
With FHR involvement (late decelerations, bradycardia, or prolonged decelerations)	70 (10.3)	18 (2.6)		<0.001*
Uterine tachysystole (non-AE)	291 (42.9)	150 (22.1)	<0.001	
Category II FHR patterns (AE)	169 (24.9)	175 (25.7)	0.755	
Category II FHR patterns (non-AE)	472 (69.6)	447 (65.7)	0.132	

(continued)

	Number (%) of Subjects			
	MVI 200 (N=678)[a]	DVI (N=680)[a]	p-value[1(a)]	p-value*
Category III FHR patterns	9 (1.3)	5 (0.7)	0.299	
Intrapartum resuscitations	85 (12.5)	66 (9.7)	0.102	
Tocolysis use	83 (12.2)	28(4.1)	<0.001	
Meconium in amniotic fluid	120 (17.7)	92 (13.5)	0.036	
Caesarean delivery during first hospitalisation	176 (26.0)	184 (27.1)	0.667	
Instrumented vaginal delivery during first hospitalisation	43 (6.3)	35 (5.1)	0.353	
Minute 1 Apgar score low (<7)	80 (11.8)	79 (11.6)	0.933	
Minute 5 Apgar score low (<7)[2]	14 (2.1)	7 (1.0)	0.130	
Intrapartum fetal acidosis	7 (1.0)[a] 8 (1.2)*	3 (0.4)[a] 4 (0.6)*	0.224	0.264*
Neonatal encephalopathy	4 (0.6)	1 (0.1)	0.217	N/A*
Neonatal ICU admissions	61 (9.0)	71 (10.4)	0.410	
Intrapartum ICU admissions	1 (0.1)	1 (0.1)	1.000	N/A*
Postpartum ICU admissions	0	0		
Postpartum hemorrhage	42 (6.2)	40 (5.9)	0.821	
Neonatal intravenous/intramuscular antibiotic use	49 (7.2) 47 (6.9)*	66 (9.7)	0.119	0.077*
Intrapartum intravenous/intramuscular antibiotic use	55 (8.1)[a] 38 (5.6)*	77 (11.3)[a] 59 (8.7)*	0.054	0.035*
Postpartum intravenous/intramuscular antibiotic use	38 (5.6)[a] 31 (4.6)*	65 (9.6)[a] (57 (8.4)*	0.007	0.006*

[1] Two-sided p-value was obtained from Fisher's exact tests. In revised analysis (data indicated by "*"), if five or fewer total subjects experienced an event, p-values were not calculated.

[2] Based on the reported 5-minute Apgar score, which differs from the AE data because Subject 18038 reported a single AE of hypoxic-ischaemic encephalopathy based on a constellation of symptoms, including low 5-minute Apgar.

* **Data** obtained by revised analysis of raw data ([a]).

Conclusions

[0074]

- MVI 200 reduced time to vaginal delivery, time to any delivery, and time to onset of active labour compared with DVI.
- MVI 200 reduced pre-delivery oxytocin use compared with DVI.
- MVI 200 had a greater percentage of subjects with vaginal delivery within 12 and 24 hours, any delivery within 12 and 24 hours, and cervical ripening success at 12 hours compared with DVI.
- Results of pharmacoeconomic endpoints demonstrated decreases in duration in L&D, percentage of subjects requiring pre-delivery oxytocin, and duration of maternal hospitalisation with MVI 200 compared with DVI.
- MVI200 reduced time of active labour compared with DVI.
- MVI200 reduced total antibiotic usage intrapartum, post-partum and neonatally compared with DVI.
- MVI200 reduced the drug dosing time compared with DVI.

[0075] The present invention relates to these new and surprising results, as set out in the claims.

Claims

1. . A method of reducing the likelihood of infection requiring use of antibiotics during or after induction of labour in a female, which comprises administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol; the likelihood of infection being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

2. A method according to claim 1, wherein the female is nulliparous.

3. A method according to claim 1, wherein the female is parous.

4. A method according to claim 1, wherein induction is because of hypertension.

5. A method according to claim 1, wherein induction is because of preeclampsia.

6. A method according to claim 1, wherein induction is because the female is post-term.

7. A method according to claim 6, wherein the female is post-term in the range 40 to 41 weeks.

8. A method according to claim 6, wherein the female is post-term in the range greater than or equal to 41 weeks.

9. A method according to claim 1, wherein induction is due to intrauterine growth restriction.

10. A method according to claim 1, wherein induction is due to premature rupture of membranes.

11. A method according to claim 1, wherein the female is provided with oxytocin for less than 8 hours during first hospitalization.

12. A method according to claim 1, wherein the infection is chorioamnionitis.

13. A method according to any preceding claim, wherein delivery is vaginal.

14. A method according to any preceding claim, wherein delivery is cesarean.

15. A method according to any preceding claim, which is intrapartum.

16. A method according to any preceding claim, which is post-partum.

17. A method according to any preceding claim, which is neonatal.

18. A method of reducing the time from start of active labour to delivery after induction of labour in a female, which comprises administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol; the time being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

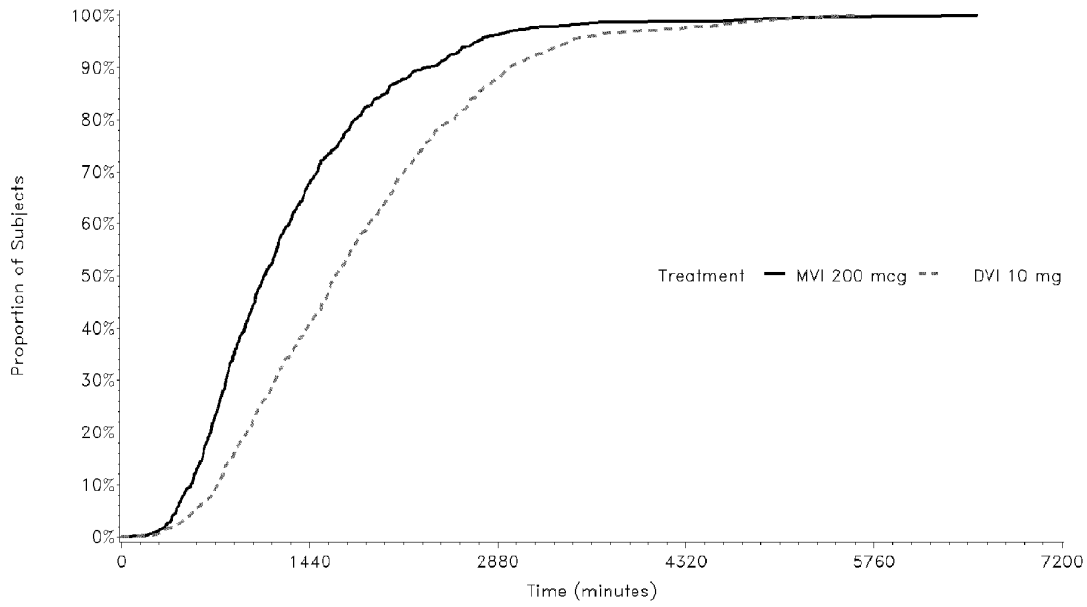
19. A method according to claim 18, wherein delivery is vaginal.

20. A method according to claim 18, wherein delivery is cesarean.

21. A method of reducing the time of drug dosing during induction of labour in a female, which comprises administering intravaginally to the female an insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate, the insert containing 200 μg misoprostol; the time being reduced in comparison to the administration of said insert containing 10 mg dinoprostone.

22. An insert comprising a cross-linked polyurethane reaction product of a polyethylene glycol, a triol and a diisocyanate and containing 200 μg misoprostol for use in the method of any preceding claim.

Figure 1: Kaplan-Meier Plot of Time to Any Delivery (All Parity)



p = < 0.001 (Two-sided Log-Rank Test)

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EUROPEAN SEARCH REPORT

Application Number
EP 13 15 0704

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X,D	WO 2011/156812 A2 (CONTROLLED THERAPEUTICS SCOTLAND LTD [GB]; POWERS BARBARA L [US]; DE L) 15 December 2011 (2011-12-15) * the whole document * -----	1-22	INV. A61K31/5575 A61P15/04
X	WING DEBORAH A ET AL: "Misoprostol Vaginal Insert for Successful Labor Induction A Randomized Controlled Trial", OBSTETRICS AND GYNECOLOGY, LIPPINCOTT WILLIAMS & WILKINS, US, vol. 117, no. 3, 1 March 2011 (2011-03-01), pages 533-541, XP009162720, ISSN: 0029-7844 * the whole document * -----	1-22	
X	Katie Silverwood: "Press Release: FERRING ANNOUNCES FDA ACCEPTANCE OF NDA FILING FOR CONTROLLED RELEASE MISOPROSTOL VAGINAL INSERT FOR DECREASING TIME TO VAGINAL DELIVERY IN WOMEN", , 23 October 2012 (2012-10-23), XP055061872, Parsippany, NJ Retrieved from the Internet: URL:http://www.ferringusa.com/news_and_events/view/88/ [retrieved on 2013-05-06] * the whole document * ----- -/--	1-22	

TECHNICAL FIELDS SEARCHED (IPC)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	10 May 2013	Paul Soto, Raquel

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EUROPEAN SEARCH REPORT

Application Number
EP 13 15 0704

DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WING DEBORAH A ET AL: "Misoprostol vaginal insert compared with dinoprostone vaginal insert a randomized controlled trial", OBSTETRICS AND GYNECOLOGY, LIPPINCOTT WILLIAMS & WILKINS, US, vol. 112, no. 4, 1 October 2008 (2008-10-01), pages 801-812, XP009162722, ISSN: 0029-7844 * the whole document * -----	1-22	

TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

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Munich	10 May 2013	Paul Soto, Raquel

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011156812 A2	15-12-2011	CA 2802214 A1	15-12-2011
		CN 102939085 A	20-02-2013
		EP 2579866 A2	17-04-2013
		WO 2011156812 A2	15-12-2011

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2004029125 A **[0003]**
- WO 2006013335 A **[0003]**
- US 4931288 A **[0005]**
- US 6642278 B **[0006]**
- US 2004044080 A **[0006]**
- WO 2003011301 A **[0006]**
- WO 2011156812 A **[0009]**

Non-patent literature cited in the description

- **POWERS et al.** *Journal of Clinical Pharmacology,* 2008, vol. 48, 26-34 **[0009]**
- **EWERT et al.** *Obstet Gynecol,* 2006, vol. 108, 1130-7 **[0009]**
- **WING et al.** *J Reprod Med,* 2008, vol. 53, 695-696 **[0009]**
- **CASTANEDA et al.** *American Jn of Obstet Gyneco,* 2005, vol. 193, 1071-5 **[0009]**
- **RAYBURN et al.** *J Soc Gynecol Investig,* 2006, vol. 13, 112-7 **[0009]**
- **PEVZNER et al.** *Obstet Gynecol,* 2009, vol. 114, 261-7 **[0009]**
- *Wing Obster Gynecol,* 2008, vol. 112, 801-12 **[0009]**
- **WING et al.** *Obstet Gynecol,* 2011, vol. 117, 533-41 **[0009]**
- **PEVZNER et al.** *Obstet Gynecol,* 2009, vol. 114, 1315-21 **[0009]**
- **PEVZNER et al.** *European J Obstet Gynecol and Repr Biology,* 2011, vol. 156, 144-148 **[0009]**