

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRACTOCILE 6.75 mg/0.9 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 0.9 ml solution contains 6.75 mg atosiban (as acetate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution without particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRACTOCILE is indicated to delay imminent pre-term birth in pregnant adult women with:

- regular uterine contractions of at least 30 seconds duration at a rate of ≥ 4 per 30 minutes
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of $\geq 50\%$
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

4.2 Posology and method of administration

Treatment with TRACTOCILE should be initiated and maintained by a physician experienced in the treatment of pre-term labour.

TRACTOCILE is administered intravenously in three successive stages: an initial bolus dose (6.75 mg), performed with TRACTOCILE 6.75 mg/0.9 ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 micrograms/min) of TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion during three hours, followed by a lower dose of TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion (subsequent infusion 100 micrograms/min) up to 45 hours. The duration of the treatment should not exceed 48 hours. The total dose given during a full course of TRACTOCILE therapy should preferably not exceed 330.75 mg of atosiban.

Intravenous therapy using the initial bolus injection should be started as soon as possible after diagnosis of pre-term labour. Once the bolus has been injected, proceed with the infusion (See Summary of Product Characteristics of TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion). In the case of persistence of uterine contractions during treatment with TRACTOCILE, alternative therapy should be considered.

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution.

The following table shows the full posology of the bolus injection followed by the infusion:

Step	Regimen	Infusion rate	Atosiban dose
1	0.9 ml intravenous bolus injection given over 1 minute	Not applicable	6.75 mg
2	3 hours intravenous loading infusion	24 ml/hour (300 µg/min)	54 mg
3	Up to 45 hours subsequent intravenous infusion	8 ml/hour (100 µg/min)	Up to 270 mg

Re-treatment

In case a re-treatment with atosiban is needed, it should also commence with a bolus injection of TRACTOCILE 6.75 mg/0.9 ml, solution for injection followed by infusion with TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion.

4.3 Contraindications

TRACTOCILE must not be used in the following conditions:

- Gestational age below 24 or over 33 completed weeks
- Premature rupture of the membranes >30 weeks of gestation
- Abnormal foetal heart rate
- Antepartum uterine haemorrhage requiring immediate delivery
- Eclampsia and severe pre-eclampsia requiring delivery
- Intrauterine foetal death
- Suspected intrauterine infection
- Placenta praevia
- Abruption placenta
- Any other conditions of the mother or foetus, in which continuation of pregnancy is hazardous
- Known hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

When atosiban is used in patients in whom premature rupture of membranes cannot be excluded, the benefits of delaying delivery should be balanced against the potential risk of chorioamnionitis.

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution (see sections 4.2 and 5.2).

There is only limited clinical experience in the use of atosiban in multiple pregnancies or the gestational age group between 24 and 27 weeks, because of the small number of patients treated. The benefit of atosiban in these subgroups is therefore uncertain.

Re-treatment with TRACTOCILE is possible, but there is only limited clinical experience available with multiple re-treatments, up to 3 re-treatments (see section 4.2).

In case of intrauterine growth retardation, the decision to continue or reinitiate the administration of TRACTOCILE depends on the assessment of fetal maturity.

Monitoring of uterine contractions and fetal heart rate during administration of atosiban and in case of persistent uterine contractions should be considered.

As an antagonist of oxytocin, atosiban may theoretically facilitate uterine relaxation and postpartum bleeding therefore blood loss after delivery should be monitored. However, inadequate uterus contraction postpartum was not observed during the clinical trials.

4.5 Interaction with other medicinal products and other forms of interaction

It is unlikely that atosiban is involved in cytochrome P450 mediated drug-drug interactions as *in vitro* investigations have shown that atosiban is not a substrate for the cytochrome P450 system, and does not inhibit the drug metabolising cytochrome P450 enzymes.

Interaction studies have been performed with labetalol and betamethasone in healthy, female volunteers. No clinically relevant interaction was found between atosiban and bethamethasone or labetalol.

4.6 Pregnancy and lactation

Atosiban should only be used when pre-term labour has been diagnosed between 24 and 33 completed weeks of gestation. If during pregnancy the woman is already breast-feeding an earlier child, then breast-feeding should be discontinued during treatment with TRACTOCILE, since the release of oxytocin during breast-feeding may augment uterine contractility, and may counteract the effect of tocolytic therapy.

In atosiban clinical trials no effects were observed on breast-feeding. Small amounts of atosiban have been shown to pass from plasma into the breast milk of breast-feeding women.

Embryo-fetal toxicity studies have not shown toxic effects of atosiban. No studies were performed that covered fertility and early embryonic development (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Possible adverse reactions of atosiban were described for the mother during the use of atosiban in clinical trials. In total 48% of the patients treated with atosiban experienced adverse reactions during the clinical trials. The observed adverse reactions were generally of a mild severity. The most commonly reported adverse reaction in the mother is nausea (14 %).

For the newborn, the clinical trials did not reveal any specific adverse reactions of atosiban. The infant adverse reactions were in the range of normal variation and were comparable with both placebo and beta-mimetic group incidences.

The frequency of adverse reactions listed below is defined using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Rare
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders		Hyperglycaemia		
Psychiatric disorder			Insomnia	
Nervous system disorders		Headache, Dizziness		
Cardiac disorders		Tachycardia		
Vascular disorders		Hypotension, Hot flush		

Gastrointestinal disorders	Nausea	Vomiting		
Skin and subcutaneous tissue disorders			Pruritis, Rash	
Reproductive system and breast disorder				Uterine haemorrhage, uterine atony
General disorders and administration site conditions		Injection site reaction	Pyrexia	

4.9 Overdose

Few cases of atosiban overdosing were reported, they occurred without any specific signs or symptoms. There is no known specific treatment in case of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynecologicals, ATC code: G02CX01

TRACTOCILE contains atosiban (INN), a synthetic peptide ([Mpa¹,D-Tyr(Et)²,Thr⁴,Orn⁸]-oxytocin) which is a competitive antagonist of human oxytocin at receptor level. In rats and guinea pigs, atosiban was shown to bind to oxytocin receptors, to decrease the frequency of contractions and the tone of the uterine musculature, resulting in a suppression of uterine contractions. Atosiban was also shown to bind to the vasopressin receptor, thus inhibiting the effect of vasopressin. In animals atosiban did not exhibit cardiovascular effects.

In human pre-term labour, atosiban at the recommended dosage antagonises uterine contractions and induces uterine quiescence. The onset of uterus relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence (≤ 4 contractions/hour) for 12 hours.

Phase III clinical trials (CAP-001 studies) include data from 742 women who were diagnosed with pre-term labour at 23–33 weeks of gestation and were randomised to receive either atosiban (according to this labelling) or β -agonist (dose-titrated).

Primary endpoint: the primary efficacy outcome was the proportion of women remaining undelivered and not requiring alternative tocolysis within 7 days of treatment initiation. The data show that 59.6% (n=201) and 47.7% (n=163) of atosiban- and β -agonist-treated women (p=0.0004), respectively, were undelivered and did not require alternative tocolysis within 7 days of starting treatment. Most of the treatment failures in CAP-001 were caused by poor tolerability. Treatment failures caused by insufficient efficacy were significantly (p=0.0003) more frequent in atosiban (n=48, 14.2%) than in the β -agonist-treated women (n=20, 5.8%).

In the CAP-001 studies the probability of remaining undelivered and not requiring alternative tocolytics within 7 days of treatment initiation was similar for atosiban and beta-mimetics treated women at gestational age of 24-28 weeks. However, this finding is based on a very small sample (n=129 patients).

Secondary endpoints: secondary efficacy parameters included the proportion of women remaining undelivered within 48 h of treatment initiation. There was no difference between the atosiban and beta-mimetic groups with regard to this parameter.

Mean (SD) gestational age at delivery was the same in the two groups: 35.6 (3.9) and 35.3 (4.2) weeks for the atosiban and β -agonist groups, respectively (p=0.37). Admission to a neonatal intensive care

unit (NICU) was similar for both treatment groups (approximately 30%), as was length of stay and ventilation therapy. Mean (SD) birth weight was 2491 (813) grams in the atosiban group and 2461 (831) grams in the β -agonist group ($p=0.58$).

Fetal and maternal outcome did apparently not differ between the atosiban and the β -agonist group, but the clinical studies were not powered enough to rule out a possible difference.

Of the 361 women who received atosiban treatment in the phase III studies, 73 received at least one re-treatment, 8 received at least 2 re-treatments and 2 received 3 re-treatments (see section 4.4).

As the safety and efficacy of atosiban in women with a gestational age of less than 24 completed weeks has not been established in controlled randomised studies, the treatment of this patient group with atosiban is not recommended (see section 4.3).

In a placebo-controlled study, fetal/infant deaths were 5/295 (1.7%) in the placebo group and 15/288 (5.2%) in the atosiban group, of which two occurred at five and eight months of age. Eleven out of the 15 deaths in the atosiban group occurred in pregnancies with a gestational age of 20 to 24 weeks, although in this subgroup patient distribution was unequal (19 women on atosiban, 4 on placebo). For women with a gestational age greater than 24 weeks there was no difference in mortality rate (1.7% in the placebo group and 1.5% in the atosiban group).

5.2 Pharmacokinetic properties

In healthy non-pregnant subjects receiving atosiban infusions (10 to 300 micrograms/min over 12 hours), the steady state plasma concentrations increased proportionally to the dose.

The clearance, volume of distribution and half-life were found to be independent of the dose.

In women in pre-term labour receiving atosiban by infusion (300 micrograms/min for 6 to 12 hours), steady state plasma concentrations were reached within one hour following the start of the infusion (mean 442 ± 73 ng/ml, range 298 to 533 ng/ml).

Following completion of the infusion, plasma concentration rapidly declined with an initial (t_{α}) and terminal (t_{β}) half-life of 0.21 ± 0.01 and 1.7 ± 0.3 hours, respectively. Mean value for clearance was 41.8 ± 8.2 litres/h. Mean value of volume of distribution was 18.3 ± 6.8 litres.

Plasma protein binding of atosiban is 46 to 48% in pregnant women. It is not known whether the free fraction in the maternal and fetal compartments differs substantially. Atosiban does not partition into red blood cells.

Atosiban passes the placenta. Following an infusion of 300 micrograms/min in healthy pregnant women at term, the fetal/maternal atosiban concentration ratio was 0.12.

Two metabolites were identified in the plasma and urine from human subjects. The ratios of the main metabolite M1 (des-(Orn⁸, Gly-NH₂⁹)-[Mpa¹, D-Tyr(Et)², Thr⁴]-oxytocin) to atosiban concentrations in plasma were 1.4 and 2.8 at the second hour and at the end of the infusion respectively. It is not known whether M1 accumulates in tissues. Atosiban is found in only small quantities in urine, its urinary concentration is about 50 times lower than that of M1. The proportion of atosiban eliminated in faeces is not known. The main metabolite M1 is approximately 10 times less potent than atosiban in inhibiting oxytocin-induced uterine contractions *in vitro*. Metabolite M1 is excreted in milk (see section 4.6).

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution (see sections 4.2 and 4.4).

It is unlikely that atosiban inhibits hepatic cytochrome P450 isoforms in humans (see section 4.5).

5.3 Preclinical safety data

No systemic toxic effects were observed during the two-week intravenous toxicity studies (in rats and dogs) at doses which are approximately 10 times higher than the human therapeutic dose, and during the three-months toxicity studies in rats and dogs (up to 20 mg/kg/day s.c.). The highest atosiban subcutaneous dose not producing any adverse effects was approximately two times the therapeutic human dose.

No studies were performed that covered fertility and early embryonic development. Reproduction toxicity studies, with dosing from implantation up to late stage pregnancy, showed no effects on mothers and fetuses. The exposure of the rat fetus was approximately four times that received by the human fetus during intravenous infusions in women. Animal studies have shown inhibition of lactation as expected from the inhibition of action of oxytocin.

Atosiban was neither oncogenic nor mutagenic in *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Hydrochloric acid 1M
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Once the vial has been opened, the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Store in the original package in order to protect from light.

6.5 Nature and contents of container

One vial of solution for injection contains 0.9 ml solution, corresponding to 6.75 mg atosiban. Colourless glass vials, clear borosilicated (type I) sealed with grey siliconised bromo-butyl rubber stopper, type I, and flip-off cap of polypropylene and aluminium.

6.6 Special precautions for disposal and other handling

The vials should be inspected visually for particulate matter and discoloration prior to administration.

Preparation of the initial intravenous injection:

Withdraw 0.9 ml of a 0.9 ml labelled vial of TRACTOCILE 6.75 mg/0.9 ml, solution for injection and administer slowly as an intravenous bolus dose over one minute, under adequate medical supervision

in an obstetric unit. The TRACTOCILE 6.75 mg/0.9 ml, solution for injection should be used immediately.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 København S
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20.01.2000

Date of latest renewal: 20.01.2010

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 5 ml solution contains 37.5 mg atosiban (as acetate).

Each ml of solution contains 7.5 mg atosiban.

After dilution, the concentration of atosiban is 0.75 mg/ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless solution without particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRACTOCILE is indicated to delay imminent pre-term birth in pregnant adult women with:

- regular uterine contractions of at least 30 seconds duration at a rate of ≥ 4 per 30 minutes
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of $\geq 50\%$
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

4.2 Posology and method of administration

Treatment with TRACTOCILE should be initiated and maintained by a physician experienced in the treatment of pre-term labour.

TRACTOCILE is administered intravenously in three successive stages: an initial bolus dose (6.75 mg), performed with TRACTOCILE 6.75 mg/0.9 ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 micrograms/min) of TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion during three hours, followed by a lower dose of TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion (subsequent infusion 100 micrograms/min) up to 45 hours. The duration of the treatment should not exceed 48 hours. The total dose given during a full course of TRACTOCILE therapy should preferably not exceed 330.75 mg of atosiban.

Intravenous therapy using the initial bolus injection of TRACTOCILE 6.75 mg/0.9 ml, solution for injection (see Summary of Product Characteristics of this product) should be started as soon as possible after diagnosis of pre-term labour. Once the bolus has been injected, proceed with the infusion. In the case of persistence of uterine contractions during treatment with TRACTOCILE, alternative therapy should be considered.

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution.

The following table shows the full posology of the bolus injection followed by the infusion:

Step	Regimen	Infusion rate	Atosiban dose
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3	Up to 45 hours subsequent intravenous infusion	8 ml/hour (100 µg/min)	Up to 270 mg

Re-treatment

In case a re-treatment with atosiban is needed, it should also commence with a bolus injection of TRACTOCILE 6.75 mg/0.9 ml, solution for injection followed by infusion with TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion.

4.3 Contraindications

TRACTOCILE must not be used in the following conditions:

- Gestational age below 24 or over 33 completed weeks
- Premature rupture of the membranes >30 weeks of gestation
- Abnormal foetal heart rate
- Antepartum uterine haemorrhage requiring immediate delivery
- Eclampsia and severe pre-eclampsia requiring delivery
- Intrauterine foetal death
- Suspected intrauterine infection
- Placenta praevia
- Abruptio placenta
- Any other conditions of the mother or foetus, in which continuation of pregnancy is hazardous
- Known hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings and precautions for use

When atosiban is used in patients in whom premature rupture of membranes cannot be excluded, the benefits of delaying delivery should be balanced against the potential risk of chorioamnionitis.

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution (see sections 4.2 and 5.2).

There is only limited clinical experience in the use of atosiban in multiple pregnancies or the gestational age group between 24 and 27 weeks, because of the small number of patients treated. The benefit of atosiban in these subgroups is therefore uncertain.

Re-treatment with TRACTOCILE is possible, but there is only limited clinical experience available with multiple re-treatments, up to 3 re-treatments (see section 4.2).

In case of intrauterine growth retardation, the decision to continue or reinstate the administration of TRACTOCILE depends on the assessment of fetal maturity.

Monitoring of uterine contractions and fetal heart rate during administration of atosiban and in case of persistent uterine contractions should be considered.

As an antagonist of oxytocin, atosiban may theoretically facilitate uterine relaxation and postpartum bleeding therefore blood loss after delivery should be monitored. However, inadequate uterus contraction postpartum was not observed during the clinical trials.

4.5 Interaction with other medicinal products and other forms of interaction

It is unlikely that atosiban is involved in cytochrome P450 mediated drug-drug interactions as *in vitro* investigations have shown that atosiban is not a substrate for the cytochrome P450 system, and does not inhibit the drug metabolising cytochrome P450 enzymes.

Interaction studies have been performed with labetalol and betamethasone in healthy, female volunteers. No clinically relevant interaction was found between atosiban and bethamethasone or labetalol.

4.6 Pregnancy and lactation

Atosiban should only be used when pre-term labour has been diagnosed between 24 and 33 completed weeks of gestation. If during pregnancy the woman is already breast-feeding an earlier child, then breast-feeding should be discontinued during treatment with TRACTOCILE, since the release of oxytocin during breast-feeding may augment uterine contractility, and may counteract the effect of tocolytic therapy.

In atosiban clinical trials no effects were observed on breast-feeding. Small amounts of atosiban have been shown to pass from plasma into the breast milk of breast-feeding women.

Embryo-fetal toxicity studies have not shown toxic effects of atosiban. No studies were performed that covered fertility and early embryonic development (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Possible adverse reactions of atosiban were described for the mother during the use of atosiban in clinical trials. In total 48% of the patients treated with atosiban experienced adverse reactions during the clinical trials. The observed adverse reactions were generally of a mild severity. The most commonly reported adverse reaction in the mother is nausea (14 %).

For the newborn, the clinical trials did not reveal any specific adverse reactions of atosiban. The infant adverse reactions were in the range of normal variation and were comparable with both placebo and beta-mimetic group incidences.

The frequency of adverse reactions listed below is defined using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Rare
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders		Hyperglycaemia		
Psychiatric disorder			Insomnia	
Nervous system disorders		Headache,		

		Dizziness		
Cardiac disorders		Tachycardia		
Vascular disorders		Hypotension, Hot flush		
Gastrointestinal disorders	Nausea	Vomiting		
Skin and subcutaneous tissue disorders			Pruritis, Rash	
Reproductive system and breast disorder				Uterine haemorrhage, uterine atony
General disorders and administration site conditions		Injection site reaction	Pyrexia	

4.9 Overdose

Few cases of atosiban overdosing were reported, they occurred without any specific signs or symptoms. There is no known specific treatment in case of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynecologicals, ATC code: G02CX01

TRACTOCILE contains atosiban (INN), a synthetic peptide ($[Mpa^1, D-Tyr(Et)^2, Thr^4, Orn^8]$ -oxytocin) which is a competitive antagonist of human oxytocin at receptor level. In rats and guinea pigs, atosiban was shown to bind to oxytocin receptors, to decrease the frequency of contractions and the tone of the uterine musculature, resulting in a suppression of uterine contractions. Atosiban was also shown to bind to the vasopressin receptor, thus inhibiting the effect of vasopressin. In animals atosiban did not exhibit cardiovascular effects.

In human pre-term labour, atosiban at the recommended dosage antagonises uterine contractions and induces uterine quiescence. The onset of uterus relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence (≤ 4 contractions/hour) for 12 hours.

Phase III clinical trials (CAP-001 studies) include data from 742 women who were diagnosed with pre-term labour at 23–33 weeks of gestation and were randomised to receive either atosiban (according to this labelling) or β -agonist (dose-titrated).

Primary endpoint: the primary efficacy outcome was the proportion of women remaining undelivered and not requiring alternative tocolysis within 7 days of treatment initiation. The data show that 59.6% (n=201) and 47.7% (n=163) of atosiban- and β -agonist-treated women (p=0.0004), respectively, were undelivered and did not require alternative tocolysis within 7 days of starting treatment. Most of the treatment failures in CAP-001 were caused by poor tolerability. Treatment failures caused by insufficient efficacy were significantly (p=0.0003) more frequent in atosiban (n=48, 14.2%) than in the β -agonist-treated women (n=20, 5.8%).

In the CAP-001 studies the probability of remaining undelivered and not requiring alternative tocolytics within 7 days of treatment initiation was similar for atosiban and beta-mimetics treated women at gestational age of 24-28 weeks. However, this finding is based on a very small sample (n=129 patients).

Secondary endpoints: secondary efficacy parameters included the proportion of women remaining undelivered within 48 h of treatment initiation. There was no difference between the atosiban and beta-mimetic groups with regard to this parameter.

Mean (SD) gestational age at delivery was the same in the two groups: 35.6 (3.9) and 35.3 (4.2) weeks for the atosiban and β -agonist groups, respectively ($p=0.37$). Admission to a neonatal intensive care unit (NICU) was similar for both treatment groups (approximately 30%), as was length of stay and ventilation therapy. Mean (SD) birth weight was 2491 (813) grams in the atosiban group and 2461 (831) grams in the β -agonist group ($p=0.58$).

Fetal and maternal outcome did apparently not differ between the atosiban and the β -agonist group, but the clinical studies were not powered enough to rule out a possible difference.

Of the 361 women who received atosiban treatment in the phase III studies, 73 received at least one re-treatment, 8 received at least 2 re-treatments and 2 received 3 re-treatments (see section 4.4).

As the safety and efficacy of atosiban in women with a gestational age of less than 24 completed weeks has not been established in controlled randomised studies, the treatment of this patient group with atosiban is not recommended (see section 4.3).

In a placebo-controlled study, fetal/infant deaths were 5/295 (1.7%) in the placebo group and 15/288 (5.2%) in the atosiban group, of which two occurred at five and eight months of age. Eleven out of the 15 deaths in the atosiban group occurred in pregnancies with a gestational age of 20 to 24 weeks, although in this subgroup patient distribution was unequal (19 women on atosiban, 4 on placebo). For women with a gestational age greater than 24 weeks there was no difference in mortality rate (1.7% in the placebo group and 1.5% in the atosiban group).

5.2 Pharmacokinetic properties

In healthy non-pregnant subjects receiving atosiban infusions (10 to 300 micrograms/min over 12 hours), the steady state plasma concentrations increased proportionally to the dose.

The clearance, volume of distribution and half-life were found to be independent of the dose.

In women in pre-term labour receiving atosiban by infusion (300 micrograms/min for 6 to 12 hours), steady state plasma concentrations were reached within one hour following the start of the infusion (mean 442 ± 73 ng/ml, range 298 to 533 ng/ml).

Following completion of the infusion, plasma concentration rapidly declined with an initial (t_{α}) and terminal (t_{β}) half-life of 0.21 ± 0.01 and 1.7 ± 0.3 hours, respectively. Mean value for clearance was 41.8 ± 8.2 litres/h. Mean value of volume of distribution was 18.3 ± 6.8 litres.

Plasma protein binding of atosiban is 46 to 48% in pregnant women. It is not known whether the free fraction in the maternal and fetal compartments differs substantially. Atosiban does not partition into red blood cells.

Atosiban passes the placenta. Following an infusion of 300 micrograms/min in healthy pregnant women at term, the fetal/maternal atosiban concentration ratio was 0.12.

Two metabolites were identified in the plasma and urine from human subjects. The ratios of the main metabolite M1 (des-(Orn⁸, Gly-NH₂⁹)-[Mpa¹, D-Tyr(Et)², Thr⁴]-oxytocin) to atosiban concentrations in plasma were 1.4 and 2.8 at the second hour and at the end of the infusion respectively. It is not known whether M1 accumulates in tissues. Atosiban is found in only small quantities in urine, its urinary concentration is about 50 times lower than that of M1. The proportion of atosiban eliminated in faeces is not known. The main metabolite M1 is approximately 10 times less potent than atosiban

in inhibiting oxytocin-induced uterine contractions *in vitro*. Metabolite M1 is excreted in milk (see section 4.6).

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys. Renal impairment is not likely to warrant a dose adjustment, since only a small extent of atosiban is excreted in the urine. In patients with impaired hepatic function, atosiban should be used with caution (see sections 4.2 and 4.4).

It is unlikely that atosiban inhibits hepatic cytochrome P450 isoforms in humans (see section 4.5).

5.3 Preclinical safety data

No systemic toxic effects were observed during the two-week intravenous toxicity studies (in rats and dogs) at doses which are approximately 10 times higher than the human therapeutic dose, and during the three-months toxicity studies in rats and dogs (up to 20 mg/kg/day s.c.). The highest atosiban subcutaneous dose not producing any adverse effects was approximately two times the therapeutic human dose.

No studies were performed that covered fertility and early embryonic development. Reproduction toxicity studies, with dosing from implantation up to late stage pregnancy, showed no effects on mothers and fetuses. The exposure of the rat fetus was approximately four times that received by the human fetus during intravenous infusions in women. Animal studies have shown inhibition of lactation as expected from the inhibition of action of oxytocin.

Atosiban was neither oncogenic nor mutagenic in *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Hydrochloric acid 1M
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

Once the vial has been opened, the dilution must be performed immediately.

Diluted solution for intravenous administration should be used within 24 hours after preparation.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Store in the original package in order to protect from light.

6.5 Nature and contents of container

One vial of concentrate for solution for infusion contains 5 ml solution, corresponding to 37.5 mg atosiban.

Colourless glass vials, clear borosilicated (type I) sealed with grey siliconised bromo-butyl rubber stopper, type I, and flip-off cap of polypropylene and aluminium.

6.6 Special precautions for disposal and other handling

The vials should be inspected visually for particulate matter and discoloration prior to administration.

Preparation of the intravenous infusion solution:

For intravenous infusion, following the bolus dose, TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion should be diluted in one of the following solutions:

- sodium chloride 9 mg/ml (0.9%) solution for injection
- Ringer's lactate solution
- 5% w/v glucose solution.

Withdraw 10 ml solution from a 100 ml infusion bag and discard. Replace it by 10 ml TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion from two 5 ml vials to obtain a concentration of 75 mg atosiban in 100 ml.

The reconstituted product is a clear, colourless solution without particles.

The loading infusion is given by infusing 24 ml/hour (i.e. 18 mg/h) of the above prepared solution over the 3 hour period under adequate medical supervision in an obstetric unit. After three hours the infusion rate is reduced to 8 ml/hour.

Prepare new 100 ml bags in the same way as described to allow the infusion to be continued.

If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation.

To achieve accurate dosing, a controlled infusion device is recommended to adjust the rate of flow in drops/min. An intravenous microdrip chamber can provide a convenient range of infusion rates within the recommended dose levels for TRACTOCILE.

If other medicinal products need to be given intravenously at the same time, the intravenous cannula can be shared or another site of intravenous administration can be used. This permits the continued independent control of the rate of infusion.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 København S
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation; 20.01.2000

Date of latest renewal: 20.01.2010

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER(S)
RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Ferring AB
Limhamnsvägen 108
20061 Limhamn
Sweden

Ferring GmbH
Wittland 11
24109 Kiel
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORITY HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

TRACTOCILE 6.75 mg/0.9 ml solution for injection
atosiban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 0.9 ml contains 6.75 mg of atosiban (as acetate)

3. LIST OF EXCIPIENTS

Mannitol, Hydrochloric acid, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
(6.75 mg/0.9 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Store in the original package in order to protect from light
Once the vial has been opened, the solution must be used immediately

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF

APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 København S
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/001

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TRACTOCILE 6.75 mg/0.9 ml injection
atosiban
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.9 ml (6.75 mg /0.9 ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion
atosiban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 5 ml contains 37.5 mg of atosiban (as acetate)
Each ml of solution contains 7.5 mg atosiban.

3. LIST OF EXCIPIENTS

Mannitol, Hydrochloric acid, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
(7.5 mg/ml)
Provides 0.75 mg/ml when diluted as recommended

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Store in the original package on order to protect from light
The diluted solution must be used within 24 hours

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 København S
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/002

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TRACTOCILE 37.5 mg/5 ml sterile concentrate
atosiban
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml (7.5 mg/ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

TRACTOCILE 6.75 mg/0.9 ml solution for injection

Atosiban

Read all of this leaflet carefully before you are given this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, midwife or pharmacist.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What TRACTOCILE is and what it is used for
2. Before you are given TRACTOCILE
3. How TRACTOCILE will be given
4. Possible side effects
5. How to store TRACTOCILE
6. Further information

1. WHAT TRACTOCILE IS AND WHAT IT IS USED FOR

TRACTOCILE contains atosiban. TRACTOCILE can be used to delay the premature birth of your baby. TRACTOCILE is used in pregnant adult women, from week 24 to week 33 of the pregnancy.

TRACTOCILE works by making the contractions in your womb (uterus) less strong. It also makes the contractions happen less often. It does this by blocking the effect of a natural hormone in your body called “oxytocin” which causes your womb (uterus) to contract.

2. BEFORE YOU ARE GIVEN TRACTOCILE

Do not use TRACTOCILE:

- If you are allergic (hypersensitive) to atosiban or any of the other ingredients of TRACTOCILE (listed in Section 6).
- If you are less than 24 weeks pregnant.
- If you are more than 33 weeks pregnant.
- If your waters have broken (premature rupture of your membranes) and you have completed 30 weeks of your pregnancy or more.
- If your unborn baby (foetus) has an abnormal heart rate.
- If you have bleeding from your vagina and your doctor wants your unborn baby to be delivered straight away.
- If you have something called “severe pre-eclampsia” and your doctor wants your unborn baby to be delivered straight away. Severe pre-eclampsia is when you have very high blood pressure, fluid retention and/or protein in your urine.
- If you have something called “eclampsia” which is similar to “severe pre-eclampsia” but you would also have fits (convulsions). This will mean your unborn baby needs to be delivered straight away.
- If your unborn baby has died.
- If you have or could have an infection of your womb (uterus).
- If your placenta is covering the birth canal.
- If your placenta is detaching from the wall of your womb.
- If you or your unborn baby have any other conditions where it would be dangerous to continue with your pregnancy.

Do not use TRACTOCILE if any of the above apply to you. If you are not sure, talk to your doctor, midwife or pharmacist before you are given TRACTOCILE.

Take special care with TRACTOCILE:

Check with your doctor, midwife or pharmacist before you are given TRACTOCILE:

- If you think your waters might have broken (premature rupture of your membranes).
- If you have kidney or liver problems.
- If you are between 24 and 27 weeks pregnant.
- If you are pregnant with more than one baby.
- If your contractions start again, treatment with TRACTOCILE can be repeated up to three more times.
- If your unborn baby is small for the time of your pregnancy.
- Your womb may be less able to contract after your baby has been born. This may cause bleeding..

If any of the above apply to you (or you are not sure), talk to your doctor, midwife or pharmacist before you are given TRACTOCILE.

Taking other medicines:

Please tell your doctor, midwife or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

3. HOW TRACTOCILE WILL BE GIVEN

TRACTOCILE will be given to you in a hospital by a doctor, nurse or midwife. They will decide how much you need. They will also make sure the solution is clear and free from particles.

TRACTOCILE will be given into a vein (intravenously) in three stages:

- The first injection of 6.75 mg in 0.9 ml will be slowly injected into your vein over one minute.
- Then a continuous infusion (drip) will be given at a dose of 18 mg per hour for 3 hours.
- Then another continuous infusion (drip) at a dose of 6 mg per hour will be given for up to 45 hours, or until your contractions have stopped.

Treatment should last no longer than 48 hours in total.

Further treatment with TRACTOCILE can be used if your contractions start again. Treatment with TRACTOCILE can be repeated up to three more times.

During treatment with TRACTOCILE, your contractions and your unborn baby's heart rate may be monitored.

It is recommended that no more than three re-treatments should be used during a pregnancy.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TRACTOCILE can cause side effects, although not everybody gets them. The side effects seen in the mother are generally of a mild severity. There are no known side effects on the unborn or new-born baby.

The following side effects may happen with this medicine:

Very common (affects more than 1 in 10 people)

- Feeling sick (nausea).

Common (affects less than 1 in 10 people)

- Headache.
- Feeling dizzy.
- Hot flushes.
- Being sick (vomiting).

- Fast heart beat.
- Low blood pressure. Signs may include feeling dizzy or light-headed.
- A reaction at the site where the injection was given.
- High blood sugar.

Uncommon (affects less than 1 in 100 people)

- High temperature (fever).
- Difficulty sleeping (insomnia).
- Itching.
- Rash.

Rare (affects less than 1 in 1,000 people)

- Your womb may be less able to contract after your baby has been born. This may cause bleeding.
- Allergic reactions.

If any of the side effects gets serious, or if you notice these or any other side effects not listed in this leaflet, please tell your doctor, midwife or pharmacist.

5. HOW TO STORE TRACTOCILE

- Keep out of the reach and sight of children.
- Do not use TRACTOCILE after the expiry date which is stated on the label EXP {MM/YYYY}. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Once the vial has been opened, the product must be used straight away.
- Do not use TRACTOCILE if you notice particulate matter and discoloration prior to administration.

6. FURTHER INFORMATION

What TRACTOCILE contains

- The active substance is atosiban.
- Each vial of TRACTOCILE 6.75 mg/0.9 ml solution for injection contains atosiban acetate equivalent to 6.75 mg of atosiban in 0.9 ml.
- The other ingredients are mannitol, hydrochloric acid and water for injections.

What TRACTOCILE looks like and contents of the pack

TRACTOCILE 6.75 mg/0.9 ml solution for injection is a clear, colourless solution without particles. One pack contains one vial containing 0.9 ml solution.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 København S
Denmark

Manufacturers:

Ferring AB
Limhamnsvägen 108

20061 Limhamn
Sweden

Ferring GmbH
Wittland 11
24109 Kiel
Germany

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

INSTRUCTION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only:
(See also section 3)

Instructions for use

Before using TRACTOCILE, the solution should be examined to ensure it is clear and free from particles.

TRACTOCILE is given intravenously in three successive stages:

- The initial intravenous injection of 6.75 mg in 0.9 ml is slowly injected into a vein over one minute.
- A continuous infusion at a rate of 24 ml/hour is given for 3 hours.
- A continuous infusion at a rate of 8 ml/hour is given for up to 45 hours, or until the contractions of the uterus have subsided.

The total duration of the treatment should be no more than 48 hours. Further treatment cycles of TRACTOCILE can be used should contractions recur. It is recommended that no more than three retreatments should be used during a pregnancy.

Preparation of the intravenous infusion

The intravenous infusion is prepared by diluting TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion in sodium chloride 9 mg/ml (0.9%) solution for injection, Ringer's lactate solution or 5% w/v glucose solution. This is done by removing 10 ml of solution from a 100 ml infusion bag and replacing it with 10 ml TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion from two 5 ml vials to obtain a concentration of 75 mg atosiban in 100 ml. If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation.

TRACTOCILE should not be mixed with other medicinal products in the infusion bag.

PACKAGE LEAFLET: INFORMATION FOR THE USER

TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion

Atosiban

Read all of this leaflet carefully before you are given this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, midwife or pharmacist.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What TRACTOCILE is and what it is used for
2. Before you are given TRACTOCILE
3. How TRACTOCILE will be given
4. Possible side effects
5. How to store TRACTOCILE
6. Further information

1. WHAT TRACTOCILE IS AND WHAT IT IS USED FOR

TRACTOCILE contains atosiban. TRACTOCILE can be used to delay the premature birth of your baby. TRACTOCILE is used in pregnant adult women, from week 24 to week 33 of the pregnancy.

TRACTOCILE works by making the contractions in your womb (uterus) less strong. It also makes the contractions happen less often. It does this by blocking the effect of a natural hormone in your body called “oxytocin” which causes your womb (uterus) to contract.

2. BEFORE YOU ARE GIVEN TRACTOCILE

Do not use TRACTOCILE:

- If you are allergic (hypersensitive) to atosiban or any of the other ingredients of TRACTOCILE (listed in Section 6).
- If you are less than 24 weeks pregnant.
- If you are more than 33 weeks pregnant.
- If your waters have broken (premature rupture of your membranes) and you have completed 30 weeks of your pregnancy or more.
- If your unborn baby (foetus) has an abnormal heart rate.
- If you have bleeding from your vagina and your doctor wants your unborn baby to be delivered straight away.
- If you have something called “severe pre-eclampsia” and your doctor wants your unborn baby to be delivered straight away. Severe pre-eclampsia is when you have very high blood pressure, fluid retention and/or protein in your urine.
- If you have something called “eclampsia” which is similar to “severe pre-eclampsia” but you would also have fits (convulsions). This will mean your unborn baby needs to be delivered straight away.
- If your unborn baby has died.
- If you have or could have an infection of your womb (uterus).
- If your placenta is covering the birth canal.
- If your placenta is detaching from the wall of your womb.
- If you or your unborn baby have any other conditions where it would be dangerous to continue with your pregnancy.

Do not use TRACTOCILE if any of the above apply to you. If you are not sure, talk to your doctor, midwife or pharmacist before you are given TRACTOCILE.

Take special care with TRACTOCILE:

Check with your doctor, midwife or pharmacist before you are given TRACTOCILE:

- If you think your waters might have broken (premature rupture of your membranes).
- If you have kidney or liver problems.
- If you are between 24 and 27 weeks pregnant.
- If you are pregnant with more than one baby.
- If your contractions start again, treatment with TRACTOCILE can be repeated up to three more times.
- If your unborn baby is small for the time of your pregnancy.
- Your womb may be less able to contract after your baby has been born. This may cause bleeding.

If any of the above apply to you (or you are not sure), talk to your doctor, midwife or pharmacist before you are given TRACTOCILE.

Taking other medicines:

Please tell your doctor, midwife or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

3. HOW TRACTOCILE WILL BE GIVEN

TRACTOCILE will be given to you in a hospital by a doctor, nurse or midwife. They will decide how much you need. They will also make sure the solution is clear and free from particles.

TRACTOCILE will be given into a vein (intravenously) in three stages:

- The first injection of 6.75 mg in 0.9 ml will be slowly injected into your vein over one minute.
- Then a continuous infusion (drip) will be given at a dose of 18 mg per hour for 3 hours.
- Then another continuous infusion (drip) at a dose of 6 mg per hour will be given for up to 45 hours, or until your contractions have stopped.

Treatment should last no longer than 48 hours in total.

Further treatment with TRACTOCILE can be used if your contractions start again. Treatment with TRACTOCILE can be repeated up to three more times.

During treatment with TRACTOCILE, your contractions and your unborn baby's heart rate may be monitored.

It is recommended that no more than three re-treatments should be used during a pregnancy

4. POSSIBLE SIDE EFFECTS

Like all medicines, TRACTOCILE can cause side effects, although not everybody gets them. The side effects seen in the mother are generally of a mild severity. There are no known side effects on the unborn or new-born baby.

The following side effects may happen with this medicine:

Very common (affects more than 1 in 10 people)

- Feeling sick (nausea).

Common (affects less than 1 in 10 people)

- Headache.
- Feeling dizzy.
- Hot flushes.
- Being sick (vomiting).
- Fast heart beat.

- Low blood pressure. Signs may include feeling dizzy or light-headed.
- A reaction at the site where the injection was given.
- High blood sugar.

Uncommon (affects less than 1 in 100 people)

- High temperature (fever).
- Difficulty sleeping (insomnia).
- Itching.
- Rash.

Rare (affects less than 1 in 1,000 people)

- Your womb may be less able to contract after your baby has been born. This may cause bleeding.
- Allergic reactions.

If any of the side effects gets serious, or if you notice these or any other side effects not listed in this leaflet, please tell your doctor, midwife or pharmacist.

5. HOW TO STORE TRACTOCILE

- Keep out of the reach and sight of children.
- Do not use TRACTOCILE after the expiry date which is stated on the label EXP {MM/YYYY}. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Store in the original package in order to protect from light.
- Dilutions for intravenous administration must be used within 24 hours after preparation.
- Do not use TRACTOCILE if you notice particulate matter and discoloration prior to administration.

6. FURTHER INFORMATION

What TRACTOCILE contains

- The active substance is atosiban.
- Each vial of TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion contains atosiban acetate equivalent to 37.5 mg of atosiban in 5 ml.
- The other ingredients are mannitol, hydrochloric acid and water for injections.

What TRACTOCILE looks like and contents of the pack

TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion is a clear, colourless solution without particles. One pack contains one vial containing 5 ml solution.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Ferring Pharmaceuticals A/S

Kay Fiskers Plads 11

2300 København S

Denmark

Manufacturers:

Ferring AB

Limhamnsvägen 108

20061 Limhamn
Sweden

Ferring GmbH
Wittland 11
24109 Kiel
Germany

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

INSTRUCTION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only:
(See also section 3)

Instructions for use

Before using TRACTOCILE, the solution should be examined to ensure it is clear and free from particles.

TRACTOCILE is given intravenously in three successive stages:

- The initial intravenous injection of 6.75 mg in 0.9 ml is slowly injected into a vein over one minute.
- A continuous infusion at a rate of 24 ml/hour is given for 3 hours.
- A continuous infusion at a rate of 8 ml/hour is given for up to 45 hours, or until the contractions of the uterus have subsided.

The total duration of the treatment should be no more than 48 hours. Further treatment cycles of TRACTOCILE can be used should contractions recur. It is recommended that no more than three retreatments should be used during a pregnancy.

Preparation of the intravenous infusion

The intravenous infusion is prepared by diluting TRACTOCILE 37.5 mg/5 ml, concentrate for solution for infusion in sodium chloride 9 mg/ml (0.9%) solution for injection, Ringer's lactate solution or 5% w/v glucose solution. This is done by removing 10 ml of solution from a 100 ml infusion bag and replacing it with 10 ml TRACTOCILE 37.5 mg/5 ml concentrate for solution for infusion from two 5 ml vials to obtain a concentration of 75 mg atosiban in 100 ml. If an infusion bag with a different volume is used, a proportional calculation should be made for the preparation.

TRACTOCILE should not be mixed with other medicinal products in the infusion bag.