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 ≥ 50%
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

4.2 Posology and method of administration

Posology

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.

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.

Patients with renal or hepatic impairment
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.

Paediatric population
The safety and efficacy of Tractocile in pregnant women aged less than 18 years have not been established. No data are available.

Method of administration

For instructions on preparation of the medicinal product before administration, see section 6.6.

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
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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.

Multiple pregnancy and medicinal products with tocolytic activity like calcium channel blockers and beta-mimetics are known to be associated with increased risk of pulmonary oedema. Therefore, atosiban should be used with caution in case of multiple pregnancy and/or concomitant administration of other medicinal products with tocolytic activity (see section 4.8).

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 Fertility, 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 (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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	

Post-marketing experience

Respiratory events like dyspnoea and pulmonary oedema, particularly in association with concomitant administration of other medicinal products with tocolytic activity, like calcium antagonists and beta-mimetics, and/or in women with multiple pregnancy, have been reported post-marketing.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-(Orn^8, Gly-NH_2^{9})-[Mpa^1, D-Tyr(Et)^2, Thr^4]-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.
For storage conditions after first opening of the medicinal product, see section 6.3.

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
Tel: +45 88 33 88 34

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2000
Date of latest renewal: 20 January 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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 ≥ 50%
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

4.2 Posology and method of administration

Posology

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.

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.

Patients with renal or hepatic impairment
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.

Paediatric population
The safety and efficacy of Tractocile in pregnant women aged less than 18 years have not been established. No data are available.

Method of administration

For instructions on preparation of the medicinal product before administration, see section 6.6.

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
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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.

Multiple pregnancy and medicinal products with tocolytic activity like calcium channel blockers and beta-mimetics are known to be associated with increased risk of pulmonary oedema. Therefore, atosiban should be used with caution in case of multiple pregnancy and/or concomitant administration of other medicinal products with tocolytic activity (see section 4.8).

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 Fertility, 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 (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥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	

Post-marketing experience

Respiratory events like dyspnoea and pulmonary oedema, particularly in association with concomitant administration of other medicinal products with tocolytic activity, like calcium antagonists and beta-mimetics, and/or in women with multiple pregnancy, have been reported post-marketing.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-(Orn^8, Gly-NH_2^{9})-[Mpa^1, D-Tyr(Et)^2, Thr^4]-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.
For storage conditions after first opening and dilution of the medicinal product, see section 6.3.

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
Tel: +45 88 33 88 34

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2000
Date of latest renewal: 20 January 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Ferring GmbH
Wittland 11
D-24109 Kiel
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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, Hydrocloric acid, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
(6.75 mg/0.9 ml)
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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
Tel: +45 88 33 88 34

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/001

13. BATCH NUMBER

Batch

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

4. BATCH NUMBER

Batch

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, Hydrocloric 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.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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
Tel: +45 88 33 88 34

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/124/002

13. BATCH NUMBER

Batch

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

4. BATCH NUMBER

Batch

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 because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, midwife or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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. What you need to know before you are given Tractocile

Do not use Tractocile:
- 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.
- if you are allergic to atosiban or any of the other ingredients of this medicine (listed in section 6).

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.

Warnings and precautions
Talk to 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 you are pregnant with more than one baby and/or are given medicines that can delay the birth of your baby, such as medicines used for high blood pressure. This may increase the risk of lung oedema (accumulation of fluid in the lungs).

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.

Children and adolescents
Tractocile has not been studied in pregnant women less than 18 years old.

Other medicines and Tractocile
Tell your doctor, midwife or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant and breast-feeding an earlier child, you should stop breast-feeding while you are given Tractocile.

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, this medicine 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 heartbeat
- 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

You may experience shortness of breath or lung oedema (accumulation of fluid in the lungs), particularly if you are pregnant with more than one baby and/or are given medicines that can delay the birth of your baby, such as medicines used for high blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor, midwife or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tractocile

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. 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 this medicine if you notice particulate matter and discoloration prior to administration.

6. Contents of the pack and other 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
Tel: +45 88 33 88 34

Manufacturer:
Ferring GmbH
Wittland 11
D-24109 Kiel
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Ferring N.V.
Tel/Tél: +32 53 72 92 00
ferringnvsa@ferring.be

България
Аквахим АД
Тел: +359 2 807 5022
aquachim@aquachim.bg

Česká republika
FerringPharmaceuticals CZ s.r.o.
Tel: +420 234 701 333
cz1-info@ferring.com

Danmark
Ferring Lægemidler A/S
Tlf: +45 88 16 88 17

Deutschland
Ferring Arzneimittel GmbH
Tel: +49 431 5852 0
info-service@ferring.de

Eesti
CentralPharma Communication OÜ
Tel: +372 601 5540
centralpharma@centralpharma.ee

Ελλάδα
Ferring Ελλάς ΜΕΠΕ

Lietuva
CentralPharma Communication UAB
Tel: +370 5 243 0444
centralpharma@centralpharma.lt

Luxembourg/Luxemburg
Ferring N.V.
Belgique/Belgien
Tel/Tél: +32 53 72 92 00
ferringnvsa@ferring.be

Magyarország
Ferring Magyarország Gyógyszerkereskedelmi Kft.
Tel: +36 1 236 3800
ferring@ferring.hu

Malta
E.J. Busuttil Ltd.
Tel: +356 21447184
info@ejbusuttil.com

Nederland
Ferring B.V.
Tel: +31 235680300
infoNL@ferring.com

Norge
Ferring Legemidler AS
Tlf: +47 22 02 08 80
mail@oslo.ferring.com

Österreich
Ferring Arzneimittel Ges.m.b.H

Τηλ: +30 210 68 43 449

España
Ferring S.A.U.
Tel: +34 91 387 70 00
registros@ferring.com

France
Ferring S.A.S.
Tél: +33 1 49 08 67 60
information.medicale@ferring.com

Hrvatska
Clinres farmacija d.o.o.
Tel: +385 1 2396 900

Ireland
Ferring Ireland Ltd.
Tel: +353 1 4637355
enquiries.ireland@ferring.com

Ísland
Vistor hf.
Sími: +354 535 70 00

Italia
Ferring S.p.A.
Tel: +39 02 640 00 11

Κύπρος
A. Potamitis Medicare Ltd
Τηλ: +357 22583333
a.potamitismedicare@cytanet.com.cy

Latvija
CentralPharma Communication SIA
Tālr: +371 674 50497
centralpharma@centralpharma.lv

Tel: +43 1 60 8080
office@ferring.at

Polska
Ferring Pharmaceuticals Poland Sp. z o.o.
Tel: +48 22 246 06 80
ferring@ferring.pl

Portugal
Ferring Portuguesa – Produtos Farmacêuticos,
Sociedade Unipessoal, Lda.
Tel: +351 21 940 51 90
geral@ferring.com

România
Ferring Pharmaceuticals Romania SRL
Tel: +40 356 113 270

Slovenija
SALUS, Veletrgovina, d.o.o.
Tel: +386 1 5899 179
regulatory@salus.si

Slovenská republika
Ferring Slovakia s.r.o.
Tel: +421 2 54 416 010
SK0-Recepcia@ferring.com

Suomi/Finland
Ferring Lääkkeet Oy
Puh/Tel: +358 207 401 440
info@ferring.fi

Sverige
Ferring Läkemedel AB
Tel: +46 40 691 69 00
info@ferring.se

United Kingdom
Ferring Pharmaceuticals Ltd.
Tel: +44 844 931 0050
contact2@ferring.com

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for 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.

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 because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, midwife or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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. What you need to know before you are given Tractocile

Do not use Tractocile:
- 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.
- if you are allergic to atosiban or any of the other ingredients of this medicine (listed in section 6).

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.

Warnings and precautions
Talk to 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 you are pregnant with more than one baby and/or are given medicines that can delay the birth of your baby, such as medicines used for high blood pressure. This may increase the risk of lung oedema (accumulation of fluid in the lungs).

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.

Children and adolescents
Tractocile has not been studied in pregnant women less than 18 years old.

Other medicines and Tractocile
Tell your doctor, midwife or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant and breast-feeding an earlier child, you should stop breast-feeding while you are given Tractocile.

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, this medicine 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 heartbeat
- 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

You may experience shortness of breath or lung oedema (accumulation of fluid in the lungs), particularly if you are pregnant with more than one baby and/or are given medicines that can delay the birth of your baby, such as medicines used for high blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor, midwife or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tractocile

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. 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 this medicine if you notice particulate matter and discoloration prior to administration.

6. Contents of the pack and other 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
Tel: +45 88 33 88 34

Manufacturer:
Ferring GmbH
Wittland 11
D-24109 Kiel
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Ferring N.V.
Tel/Tél: +32 53 72 92 00
ferringnvsa@ferring.be

България
Аквахим АД
Тел: +359 2 807 5022
aquachim@aquachim.bg

Česká republika
Ferring Pharmaceuticals CZ s.r.o.
Tel: +420 234 701 333
cz1-info@ferring.com

Danmark
Ferring Lægemidler A/S
Tlf: +45 88 16 88 17

Deutschland
Ferring Arzneimittel GmbH
Tel: +49 431 5852 0
info-service@ferring.de

Eesti
CentralPharma Communication OÜ
Tel: +372 601 5540
centralpharma@centralpharma.ee

Ελλάδα
Ferring Ελλάς ΜΕΠΕ
Τηλ. +30 210 68 43 449

Lietuva
CentralPharma Communication UAB
Tel.: +370 5 243 0444
centralpharma@centralpharma.lt

Luxembourg/Luxemburg
Ferring N.V.
Belgique/Belgien
Tel/Tél: +32 53 72 92 00
ferringnvsa@ferring.be

Magyarország
Ferring Magyarország Gyógyszerkereskedelmi Kft.
Tel: +36 1 236 3800
ferring@ferring.hu

Malta
E.J. Busuttil Ltd.
Tel: +356 21447184
info@ejbusuttil.com

Nederland
Ferring B.V.
Tel: +31 235680300
infoNL@ferring.com

Norge
Ferring Legemidler AS
Tlf: +47 22 02 08 80
mail@oslo.ferring.com

Österreich
Ferring Arzneimittel Ges.m.b.H
Tel: +43 1 60 8080
office@ferring.at

España
Ferring S.A.U.
Tel: +34 91 387 70 00
registros@ferring.com

France
Ferring S.A.S.
Tél: +33 1 49 08 67 60
information.medicale@ferring.com

Hrvatska
Clinres farmacija d.o.o.
Tel: +385 1 2396 900

Ireland
Ferring Ireland Ltd.
Tel: +353 1 4637355
enquiries.ireland@ferring.com

Ísland
Vistor hf.
Sími: +354 535 70 00

Italia
Ferring S.p.A.
Tel: +39 02 640 00 11

Κύπρος
A. Potamitis Medicare Ltd
Τηλ: +357 22583333
a.potamitismedicare@cytanet.com.cy

Latvija
CentralPharma Communication SIA
Tālr: +371 674 50497
centralpharma@centralpharma.lv

Polska
Ferring Pharmaceuticals Poland Sp. z o.o.
Tel: +48 22 246 06 80
ferring@ferring.pl

Portugal
Ferring Portuguesa – Produtos Farmacêuticos,
Sociedade Unipessoal, Lda.
Tel: +351 21 940 51 90
geral@ferring.com

România
Ferring Pharmaceuticals Romania SRL
Tel: +40 356 113 270

Slovenija
SALUS, Veletrgovina, d.o.o.
Tel: +386 1 5899 179
regulatory@salus.si

Slovenská republika
Ferring Slovakia s.r.o.
Tel: +421 2 54 416 010
SK0-Recepcia@ferring.com

Suomi/Finland
Ferring Lääkkeet Oy
Puh/Tel: +358 207 401 440
info@ferring.fi

Sverige
Ferring Läkemedel AB
Tel: +46 40 691 69 00
info@ferring.se

United Kingdom
Ferring Pharmaceuticals Ltd.
Tel: +44 844 931 0050
contact2@ferring.com

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for 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.