APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

Tractocile® 7,5 mg/ml concentrate for solution for infusion.

Tractocile® 7,5 mg/ml solution for injection.

COMPOSITION:

One ml solution contains 7,5 mg atosiban free base in the form of atosiban acetate.

After dilution of **Tractocile®** 7,5 mg/ml concentrate for solution for infusion, the concentration of atosiban is 0,75 mg/ml.

PHARMACOLOGICAL CLASSIFICATION:

A 18.9 Uterine antispasmodics

PHARMACOLOGICAL ACTION:

Pharmacodynamics

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 which decreased 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. Atosiban did not exhibit cardiovascular effects in animals.

In human pre-term labour, atosiban at the recommended dosage inhibits uterine contractions and induces uterine quiescence in 59,6 % of patients. The onset of uterus relaxation following atosiban is rapid with uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence (≤ 4 contractions / hour) for 12 hours.

Pharmacokinetics

In healthy non-pregnant subjects receiving **Tractocile®** infusion (10 to 300 μg/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 **Tractocile®** by intravenous infusion (300 μg/min for 6 to 12 hours), steady 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 l/h. Mean value of volume of distribution was 18,3 ± 6,81 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 foetal compartments differ substantially.

Atosiban does not partition into red blood cells.

Atosiban passes through the placenta. Following an infusion of 300 μg/min in healthy pregnant women at term, the foetal/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. Metabolite M1 is apparently as potent as the parent compound in inhibiting oxytocin-induced uterine contractions *in vitro*. Metabolite M1 is excreted in breast milk.

There is no experience with **Tractocile®** treatment in patients with impaired function of the liver or kidneys.

It is not known whether atosiban inhibits hepatic cytochrome P_{450} isoforms in humans.

INDICATIONS:

Tractocile® is indicated for short term use to delay imminent pre-term birth in pregnant women with:

- a gestational age from 26 completed weeks until 33 completed weeks;
- regular uterine contractions of at least 30 seconds duration at a rate of $\geq$ 4 per 30 minutes;
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of $\geq$ 50 %;
- a foetus without signs of foetal distress.

CONTRA-INDICATIONS:

Tractocile® should not be used in the following conditions:

- Gestational age below 26 completed weeks or over 33 completed weeks, as there was increased foetal mortality
- Premature rupture of the membranes > 30 weeks of gestation
- Intrauterine growth restriction and abnormal foetal heart rate
- Eclampsia and severe pre-eclampsia
- 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.

WARNINGS:

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

There is no experience with **Tractocile®** treatment in patients with impaired function of the liver or kidneys.

Tractocile® has not been used in patients with an abnormal placental site.

There is only limited clinical experience in the use of **Tractocile®** in multiple pregnancies or the gestational age group between 24 and 27 weeks, because of the small number of patients treated. The benefit of **Tractocile®** 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 Dosage and Directions for use).

During administration of **Tractocile®** it is advisable to monitor uterine contractions and foetal heart rate.

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.

Tractocile® should only be used when pre-term labour has been diagnosed between 26 and 33 completed weeks of gestation.

DOSAGE AND DIRECTIONS FOR USE:

Treatment with **Tractocile®** should be initiated and maintained by a medical practitioner 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®** 7,5 mg/ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 μg/min) of **Tractocile®** 7,5 mg/ml concentrate for solution for infusion during three hours, followed by a lower dose of **Tractocile®** 7,5 mg/ml concentrate for solution for infusion (subsequent infusion 100 μg/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 mg of the active substance.

Intravenous therapy using the initial bolus injection of **Tractocile®** 7,5 mg/ml solution for injection 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 data available regarding the need for dose adjustments in patients with renal or liver insufficiency.

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

Step	**Regimen**	**Injection/infusion rate**	**Atosiban dose**
1	0,9 ml intravenous bolus	over 1 minute	6,75 mg
2	3 hours intravenous loading infusion	24 ml/hour	18 mg/hour
3	subsequent intravenous infusion	8 ml/hour	6 mg/hour

Instructions for use and handling (injection)

Withdraw 0,9 ml of a 0,9 ml labelled vial of **Tractocile®** 7,5 mg/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®** 7,5 mg/ml solution for injection should be used immediately. Any unused portion should be discarded.

Instructions for use and handling (infusion)

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

Preparation of the intravenous infusion/injection solution:

For intravenous infusion, following the bolus dose, **Tractocile®** 7,5 mg/ml concentrate for solution for infusion should be diluted in one of the following solutions:

- 0,9 % w/v NaCI
- Ringer's lactate solution
- 5 % w/v glucose solution

Withdraw 10 ml solution from a 100 ml infusion bag and discard. Replace it with 10 ml **Tractocile®** 7,5 mg/ml concentrate for solution for infusion from two 5 ml vials to obtain a concentration of 75 mg atosiban in 100 ml. 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. 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.

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products. If other medicinal products need to be given intravenously at the same time, the same intravenous cannula can be used or another site of intravenous

administration can be used. This permits the continued independent control of the rate of infusion.

Re-treatment

In case a re-treatment with **Tractocile®** is needed, it should also commence with a bolus injection of **Tractocile®** 7,5 mg/ml solution for injection followed by infusion with **Tractocile®** 7,5 mg/ml concentrate for solution for infusion.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects

Undesirable effects for the mother during the use of **Tractocile®** in clinical trials were reported. The observed undesirable effects were generally of a mild severity.

A total of 48 % of the patients treated with **Tractocile®** experienced undesirable effects.

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

Undesirable effects in the women were the following:

Very common (> 10 %): Nausea

Common (1-10 %): *Central & peripheral nervous system disorders:*

headache, dizziness

Body as a whole – general disorders:

hot flushes

Gastro-intestinal system disorders:

vomiting

Cardiovascular disorders:

tachycardia, hypotension

Application site disorders:

injection site reaction

Metabolic and nutritional disorders:

hyperglycaemia

Uncommon (0,1- 1 %): *Body as a whole – general disorders:*

fever

Psychiatric disorders:

insomnia

Skin and appendages disorders:

pruritis, rash

Rare (< 0,1 %): Incidental cases of uterine haemorrhage/uterine atony were reported. The frequency did not exceed that of the control groups in clinical trials.

Special Precautions

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See "Side-Effects and Special Precautions". There is no known specific treatment in case of an overdose. Treatment is symptomatic and supportive.

IDENTIFICATION:

Clear, colourless solution free from visible particles.

PRESENTATION:

Tractocile® 7,5 mg/ml concentrate for solution for infusion.

5 ml clear, colourless glass vials, sealed with grey rubber stopper, type I, and flip-off cap of polypropylene and aluminium.

Tractocile® 7,5 mg/ml solution for injection.

2 ml clear, colourless glass vials containing 0,9 ml solution, sealed with grey rubber stopper, and flip-off cap of polypropylene and aluminium.

STORAGE INSTRUCTIONS:

Refrigerate at 2 – 8ºC.

Store in original container and protect from light.

Discard any unused portion.

Concentrate for solution for infusion:

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.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

Tractocile® 7,5 mg/ml (5 ml) concentrate for solution for infusion : 36/18.9/0336

Tractocile® 7,5 mg/ml (0,9 ml) solution for injection : 36/18.9/0335

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

FERRING (PTY) LIMITED

Route 21 Corporate Park

6 Regency Drive

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South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

7 February 2003

Tractocile® 7,5 mg/ml (5 ml) concentrate for solution for infusion:

Namibia S2 Reg No/Nr: 10/18.9/0426

Botswana S2 Reg No/Nr: BOT1302386

Tractocile® 7,5 mg/ml (0,9 ml) solution for injection:

Namibia S2 Reg No/Nr: 10/18.9/0425

Botswana S2 Reg No/Nr: BOT1302385