SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Tractocile® Solution for injection 7,5 mg/ml (6,75 mg/0,9 ml).

Tractocile® Concentrate for solution for infusion 7,5 mg/ml (37,5mg/5 ml).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tractocile® Solution for injection: Each vial of 0,9 ml solution contains 6,75 mg atosiban (as acetate).

Tractocile® Concentrate for solution for infusion: Each vial of 5 ml solution contains 37,5 mg atosiban (as acetate).

Each ml of solution contains 7,5 mg atosiban (as acetate).

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

Contains sugar.

Tractocile® Solution for injection: Contains mannitol 45 mg per vial.

Tractocile® Concentrate for solution for infusion: Contains mannitol 250 mg per vial.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tractocile® Solution for injection.

Tractocile® Concentrate for solution for infusion.

Clear, colourless solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 ≥ 4 per 30 minutes;
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of ≥ 50 %;
- a foetus without signs of foetal distress.

4.2 Posology and method of administration

Posology

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® Solution for injection** 6,75 mg/0,9 ml, immediately followed by a continuous high dose infusion (loading infusion 300 µg/min) of **Tractocile® Concentrate for solution for infusion** 37,5 mg/5 ml mg/ml during three hours, followed by a lower dose of **Tractocile® Concentrate for solution for infusion** 37,5 mg/5 ml (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® Solution for injection** 6,75 mg/0,9 ml 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

Re-treatment

In case a re-treatment with **Tractocile®** is needed, it should also commence with a bolus injection of **Tractocile® Solution for injection** 6,75 mg/0,9 ml followed by infusion with **Tractocile® Concentrate for solution for infusion** 37,5 mg/5 ml.

Special populations

Patients with renal or hepatic impairment

There is no experience with **Tractocile®** 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, **Tractocile®** should be used with caution (see section 4.4 and 5.2).

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 medicine before administration, see section 6.6.

4.3 Contraindications

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
- Antepartum uterine haemorrhage requiring immediate delivery
- 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.

4.4 Special warnings and precautions for use

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. 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).

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 because of the small number of patients treated. The benefit of **Tractocile®** in this subgroup 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 Posology and method of administration).
In case of intrauterine growth retardation, the decision to continue or reinitiate the administration of **Tractocile®** depends on the assessment of foetal maturity.

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.

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

4.5 Interaction with other medicines and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

If during pregnancy the woman is already breastfeeding an earlier child, then breastfeeding should be discontinued during treatment with **Tractocile®**, since the release of oxytocin during breastfeeding may augment uterine contractility, and may counteract the effect of tocolytic therapy.

In atosiban clinical trials no effects were observed on breastfeeding. Small amounts of atosiban have been shown

to pass from plasma into the breast milk of breastfeeding women.

Fertility

Embryo-foetal toxicity studies have not shown toxic effects of atosiban. No studies were performed that covered fertility and early embryonic development.

4.7 Effects on ability to drive and use machines

Atosiban may cause dizziness. Patients experiencing dizziness should not drive or use machines.

4.8 Undesirable 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. The most commonly reported adverse reaction in the mother is nausea (14 %).

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.

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.

Immune system disorders

Rare: Allergic reaction

Metabolism and nutrition disorders

Common: Hyperglycaemia

Psychiatric disorders

Uncommon: Insomnia

Nervous system disorders

Common: Headache, dizziness

Cardiac disorders

Common: Tachycardia

Vascular disorders

Common: Hypotension, hot flush

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting

Skin and subcutaneous tissue disorders

Uncommon: Pruritis, rash

Reproductive system and breast disorders

Rare: Uterine haemorrhage, uterine atony

General disorders and administration site conditions

Common: Injection site reaction

Uncommon: 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 during post-marketing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **Tractocile®** is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8 Undesirable effects. There is no known specific treatment in case of an overdose. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynaecological, 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 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.

5.2 Pharmacokinetic properties

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 (see section 4.6).

There is no experience with **Tractocile®** treatment in patients with impaired function of the liver or kidneys (see section 4.2 and 4.4).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Hydrochloric acid 1M (for pH adjustment)

Water for injection

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product should 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 product must be used immediately.

Tractocile® 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.

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

Tractocile® 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.

Tractocile® 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.

6.6 Special precautions for disposal and other handling

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

Tractocile® Solution for injection

Withdraw 0,9 ml of a 0,9 ml labelled vial of **Tractocile® Solution for injection** and administer slowly as an intravenous bolus dose over one minute, under adequate medical supervision in an obstetric unit. The **Tractocile® Solution for injection** should be used immediately. Any unused portion should be discarded.

Tractocile® Concentrate for solution for infusion

Preparation of the intravenous infusion solution:

For intravenous infusion, following the bolus dose, **Tractocile® 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® 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. 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.

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.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

FERRING (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene Ext 30

South Africa

8 REGISTRATION NUMBERS

Tractocile® Solution for injection: 36/18.9/0335

Tractocile® Concentrate for solution for infusion: 36/18.9/0336

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

7 February 2003

10 DATE OF REVISION OF TEXT

25 September 2022

Tractocile® Solution for injection:

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

Botswana S2 Reg No/Nr: BOT1302385

Tractocile® Concentrate for solution for infusion:

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

Botswana S2 Reg No/Nr: BOT1302386