Tractocile®
7.5 mg/ml Concentrate for solution for infusion
INN name: atosiban

The active substance is atosiban.
The other ingredients are mannitol, hydrochloric acid and water for injections.
Pharmacotherapeutic group: Other gynecologicals, ATO code: G02CX01

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine
- This leaflet contains practical information on Tractocile®
- Keep this leaflet. You may need to read it again
  Should you have any question or if you are not sure about anything, please ask your doctor or your pharmacist.
- Tractocile® is a medicinal product to be used in hospital and should only be administered under supervision of experienced hospital personnel.

Pharmaceutical Form
Concentrate solution for infusion. Each vial contains 37.5mg atosiban

Therapeutic indications
Tractocile® is indicated to delay imminent pre-term birth in pregnant 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%
- age ≥ 18 years
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

Posology and method of administration
Treatment with Tractocile® should be initiated and maintained by a physician experienced in the treatment of preterm labour.

Tractocile® is administered intravenously in three successive stages: an initial bolus dose (6.75mg), performed with Tractocile® 7.5 mg/ml solution for injection, immediately followed by continuous high dose infusion (loading infusion 300 µg/min) of Tractocile® 7.5mg/ml concentrate for solution for infusion during three hours, followed by a lower dose of Tractocile® 7.5mg/ml concentrate for solution for infusion (subsequent infusion 100µg/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 330mg of the active substance.
Intravenous therapy using the initial bolus injection should be started as soon as possible after diagnosis of preterm 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 of dose adjustments in patients with renal or liver insufficiency.

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Regimen</th>
<th>Injection/infusion rate</th>
<th>Atosiban dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 ml intravenous bolus</td>
<td>Over 1 minute</td>
<td>6.75 mg</td>
</tr>
<tr>
<td>2</td>
<td>3 hours intravenous loading infusion</td>
<td>24 ml/hour</td>
<td>18 mg/hour</td>
</tr>
<tr>
<td>3</td>
<td>Subsequent intravenous infusion</td>
<td>8 ml/hour</td>
<td>6 mg/hour</td>
</tr>
</tbody>
</table>

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.

**Contraindications**
Tractocile® should 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
- Intrauterine growth retardation and abnormal foetal heart rate
- Antepartum uterine haemorrhage requiring immediate delivery
- Eclampsia and severe pre-eclampsia requiring delivery
- Intrauterine foetal death
- Suspected intrauterine infection
- Placenta praevia
- Abruption placenta
- Any other conditions of the mother or foetus, in which continuation of pregnancy is hazardous
- Known hypersensitivity to the active substance or any of the excipients.

**Special Warnings and Precaution for use**
When Tractocile® 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
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. In case of intrauterine growth retardation, the decision to continue or reinitiate the administration of Tractocile® depends on the assessment of foetal maturity.

Monitoring of uterine contractions and foetal heart rate during administration of Tractocile® 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 post partum was not observed during the clinical trials.

**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 were performed in healthy, female volunteers with betamethasone and labetalol. No clinically relevant interaction was observed between Tractocile® and betamethasone. When Tractocile® and labetalol were co-administered, Cmax of labetalol was decreased by 36% and Tmax increased by 45 minutes. However, the extent of labetalol bioavailability in terms of AUC did not change. The interaction observed has no clinical relevance. Labetalol had no effect on Tractocile® pharmacokinetics.

No interaction study has been performed with antibiotics, ergot alkaloids, and anti-hypertensive agents other than labetalol.

**Pregnancy and lactation**

Tractocile® should only be used when preterm labour has been diagnosed between 24 and 33 completed weeks of gestation.

In Tractocile® 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.

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

**Effects on ability to drive and use machines**

Not applicable
**Undesirable effects**

Possible undesirable effects of atosiban were described for the mother during the use of Tractocile® in clinical trials. The observed undesirable effects were generally of a mild severity. In total 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.

The undesirable effects in the women were the following:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very (&gt;10%)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Common (1-10%)</td>
<td>Central &amp; peripheral nervous system disorders: headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Body as a whole - general disorders: Hot flushes</td>
</tr>
<tr>
<td></td>
<td>Gastro-intestinal system disorders: vomiting</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disorders: tachycardia, hypotension</td>
</tr>
<tr>
<td></td>
<td>Application site disorders: injection site reaction</td>
</tr>
<tr>
<td></td>
<td>Metabolic and nutritional disorders: hyperglycaemia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Body as a whole - general disorders: fever</td>
</tr>
<tr>
<td>(0.1-1%)</td>
<td>Psychiatric disorders: insomnia</td>
</tr>
<tr>
<td></td>
<td>Skin and appendages disorders: pruritis, rash</td>
</tr>
<tr>
<td>Rare (&lt;0.1%)</td>
<td>Incidental cases of uterine haemorrhage/uterine atony were reported. The frequency did not exceed that of the control groups in clinical trials. One case of allergic reaction was reported, which was considered to be probably related to atosiban</td>
</tr>
</tbody>
</table>

**Overdose**

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

**Pharmacological properties**

**Pharmacodynamic properties**

In human preterm labour, atosiban at the recommended dosage antagonises uterine contractions and induces uterine quiscence. 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.

**Pharmacokinetic properties**

In healthy non-pregnant subjects receiving Tractocile infusions (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 preterm labour receiving Tractocile by infusion (300 µg/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 ($t_\alpha$) and terminal ($t_\beta$) 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 ± 6.8 l.
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 differs substantially. Atosiban does not partition into red blood cells.

Atosiban passes 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\textsuperscript{8}, Gly-NH\textsubscript{2}\textsuperscript{9})-[Mpa\textsuperscript{1}, D-Tyr(Et)\textsuperscript{2}, Thr\textsuperscript{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. Main metabolite M1 is apparently as potent as the parent compound in inhibiting oxytocin-induced uterine contractions in vitro. Metabolite M1 is excreted in milk (see section 4.6, Pregnancy and Lactation).

There is no experience with Tractocile treatment in patients with impaired function of the liver or kidneys (see sections 4.2, Posology and method of administration and 4.4, Special warnings and precautions for use).

It is unlikely that atosiban inhibits hepatic cytochrome P450 isoforms in humans (see section 4.5 Interaction with other medicinal products and other forms of interaction).

**Incompatibilities**
In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products.

**Shelf life**
2 years. Once the vial has been opened, the product must be used immediately. Diluted solution for intravenous administration should be used within 24 hours after preparation.

**Special precautions for storage**
Store at 2-8\textdegree C. Store in original container.

**Nature and contents of container**
One vial of solution for injection contains 5 ml. 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.

**Instructions for use and handling**
The vials should be inspected visually for particulate matter and discolouration prior to administration.

**Preparation for intravenous infusion solution:**
For intravenous infusion, following the bolus dose, Tractocile\textsuperscript{®} 7.5 mg/ml, concentrate for solution for infusion should be diluted in one of the following solutions:

- 0.9% w/v NaCl
- Ringer's lactate
- solution
Withdraw 10 ml solution from a 100 ml infusion bag and discard. Replace it by 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 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 infusion rates within the recommended dose levels for Tractocile®.

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 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.

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