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TRACTOCILE®
7.5 mg/ml solution for injection
7.5 mg/ml concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection
One ml solution contains 7.5 mg atosiban free base in the form of atosiban acetate.

Concentrate for solution for infusion
One ml solution contains 7.5 mg atosiban free base in the form of atosiban acetate.

After dilution according to the instructions in INSTRUCTIONS FOR USE AND HANDLING, the concentration of atosiban is 0.75 mg/ml.

Excipients: Mannitol, hydrochloric acid 1M and water for injections.

PHARMACEUTICAL FORM

Solution for injection
Solution for injection. Each vial contains 6.75 mg atosiban.

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

THERAPEUTIC INDICATIONS

TRACTOCILE® is indicated to delay imminent preterm 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 28 until 33 completed weeks
- a normal fetal 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.

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 preterm labour. Once the bolus has been injected, proceed with the infusion.

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.

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® 7.5 mg/ml, solution for injection followed by infusion with TRACTOCILE® 7.5 mg/ml, concentrate for solution for infusion.

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CONTRAINDICATIONS

TRACTOCILE® should not be used in the following conditions:

- Gestational age below 28 or over 33 completed weeks
- Premature rupture of the membranes > 30 weeks of gestation
- Intrauterine growth retardation and abnormal fetal heart rate
- Antepartum uterine haemorrhage requiring immediate delivery
- Eclampsia and severe pre-eclampsia requiring delivery
- Intrauterine fetal death
- Suspected intrauterine infection
- Placenta praevia
- Abruptio placenta
- Any other conditions of the mother or fetus, in which continuation of pregnancy is hazardous
- Known hypersensitivity to the active substance or any of the excipients

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 (see sections POSOLOGY AND METHOD OF ADMINISTRATION and PHARMACOKINETIC PROPERTIES).

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

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 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 section 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 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 post-partum bleeding, therefore blood loss after delivery should be monitored. However, inadequate uterus contraction post-partum was not observed during the clinical trials.

Multiple pregnancy and tocolytics like calcium channel blockers and betamimetics are known to be associated with increased risk of pulmonary oedema. Therefore atosiban should be used with caution in case of multiple gestations and/or concomitant administration of other tocolytics.

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 atosiban and betamethasone. When atosiban and labetalol were co-administered, C_{max} of labetalol was decreased by 36% and T_{max} 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 atosiban pharmacokinetics.

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

PREGNANCY AND LACTATION

Atosiban should only be used when preterm labour has been diagnosed between 28 and 33 completed weeks of gestation.

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In atosiban 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 (see section PRECLINICAL SAFETY DATA).

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 atosiban in clinical trials. The observed undesirable effects were generally of a mild severity. In total 48% of the patients treated with atosiban 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:

MedDRA Organ Class	**Very common (≥10%)**	**Common (≥1- <10%)**	**Uncommon (≥0.1- <1%)**	**Rare (≥0.01- <0.1%)**	**Very rare (<0.01%)**
Immune system disorders					Hypersensitivity
Metabolism and nutrition disorders		Hyperglycaemia			
Psychiatric disorders			Insomnia		
Nervous system disorders		Headache, dizziness			
Cardiac disorders		Tachycardia			
Vascular disorders		Hypotension			
Gastrointestinal disorders	Nausea	Vomiting			
Skin and subcutaneous tissue disorders			Pruritus, rash		
Reproductive system and breast disorders				Uterine haemorrhage ,uterine atony	
General disorders and administration site conditions		Hot flushes, injection site reaction	Fever		

Respiratory events like dyspnoea and pulmonary oedema, particularly in association with concomitant administration of other tocolytics like calcium antagonists and beta-mimetics and/or multiple pregnancy, have been reported during the post-marketing.

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.

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 preterm labour, atosiban at the recommended dosage antagonises uterine contractions and induces uterine quiescence. The onset of uterine 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) included data from 742 women who were diagnosed with preterm labour at 23-33 weeks of gestation and were randomised to receive either atosiban (according to this labelling) or ß-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 ß-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 ß-agonist treated women (n=20, 5.8%).
In the CAP-001 studies the probability of remaining undelivered and not requiring alternative tocolysis 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 ß-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) g in the atosiban group and 2461 (831) g in the ß-agonist group (p=0.58).

Fetal and maternal outcome did apparently not differ between the atosiban and the ß-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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 CONTRAINDICATIONS).

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 exposed to atosiban at 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 exposed at 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).

PHARMACOKINETIC PROPERTIES
In healthy non-pregnant subjects receiving atosiban 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 atosiban 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_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 1/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 fetal compartments differ substantially.

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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 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-NH2^{9})-[Mpa^{1}, D-Tyre(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 PREGNANCY AND LACTATION).

There is no experience with atosiban treatment in patients with impaired function of the liver or kidneys (see section POSOLOGY AND METHOD OF ADMINISTRATION and SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

It is unlikely that atosiban inhibits hepatic cytochrome P450 isoforms in humans (see section INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

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.

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

SHELF LIFE
4 years

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

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.

SPECIAL PRECAUTIONS FOR STORAGE
Store at 2°C – 8°C. Store in the original container.

PACK SIZES
Solution for injection
One vial of solution for injection contains 0.9 ml.

Concentrate for solution for infusion
One vial of concentrate for solution for infusion contains 5 ml.

INSTRUCTIONS FOR USE AND HANDLING
Solution for injection
The vials should be inspected visually for particulate matter and discoloration prior to administration.

Preparation of the initial intravenous injection

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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.

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products (see section INCOMPATIBILITIES).

Concentrate for solution for infusion

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® 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
- 5% w/v glucose 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 flow in drops/min. An intravenous microdrip chamber can provide a convenient range 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 the infusion.

MANUFACTURER

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