

TRACTOCILE

Atosiban acetate

Presentation

Injection

TRACTOCILE 7.5mg/ml solution for injection. One ml solution contains 7.5mg atosiban free base in the form of atosiban acetate. A clear, colourless solution, free from visible particles. Each 0.9ml vial contains 6.75mg atosiban.

Infusion

TRACTOCILE 7.5mg/ml concentrate for dilution for infusion. One ml solution contains 7.5mg atosiban free base in the form of atosiban acetate. A clear, colourless solution, free from visible particles. Each 5ml vial contains 37.5mg atosiban. After dilution, according to the instructions under **Instructions for Use and Handling**, the concentration of atosiban is 0.75mg/ml.

Uses

Actions

Pharmacotherapeutic group: Other gynaecologicals, ATC code G02CX01

TRACTOCILE contains atosiban (INN), a synthetic peptide ([Mpa¹,D-Tyr(Et)²,Thr₄,Orn⁸]-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 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 preterm labour at 23-33 weeks of gestation and were randomised to receive either TRACTOCILE (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 hours 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 2491g (813) in the atosiban group and 2461g (831) in the β -agonist group ($p=0.58$).

Foetal and maternal outcome did not apparently 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 TRACTOCILE 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 **WARNINGS AND PRECAUTIONS**).

As the safety and efficacy of TRACTOCILE 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 TRACTOCILE is not recommended (see **CONTRAINDICATIONS**).

In a placebo-controlled study, foetal/infant deaths were 5/295 (1.7%) in the placebo group and 15/288 (5.2%) in the TRACTOCILE group, of which two occurred at five and eight months of age. Eleven out of the 15 deaths in the TRACTOCILE group occurred in pregnancies with a gestational age of 20 to 24 weeks, although in this subgroup patient distribution was unequal (19 women on TRACTOCILE, 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 TRACTOCILE group).

Pharmacokinetics

In healthy non-pregnant subjects receiving TRACTOCILE infusions (10 to 300 μ g/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 μ g/min for 6 to 12 hours), steady state plasma concentrations were reached within one hour following the start of the infusion (mean 442 \pm 73ng/ml, range 298 to 533ng/ml).

Following completion of the infusion, plasma concentration rapidly declined with an initial (t_{α}) and terminal (t_{β}) half-life of 0.21 \pm 0.01 and 1.7 \pm 0.3 hours respectively. Mean value for clearance was 41.8 \pm 8.2 l/h. Mean value of volume of distribution was 18.3 \pm 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 foetal compartments differs substantially. Atosiban does not partition into red blood cells.

Atosiban passes the placenta. Following an infusion of 300 μ g/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-(Orn⁸, Gly-NH₂⁹)-[Mpa¹, D-Tyr(Et)², Thr⁴]-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 approximately 10 times less potent than atosiban in inhibiting oxytocin-induced uterine contractions *in vitro*. Metabolite M1 is excreted in milk (see **Use During Pregnancy**).

There is no experience with TRACTOCILE treatment in patients with impaired function of the liver or kidneys (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

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

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 1cm to 3cm (0-3 for nulliparas) and effacement of $\geq 50\%$
- age ≥ 18 years
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

Dosage and Administration

Note 1: This product must only be used in facilities with resuscitative mechanisms.

Note 2: **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 (6.75mg), performed with TRACTOCILE 7.5mg/ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 μ g/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 100 μ g/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 of TRACTOCILE 7.5mg/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	0.9ml intravenous bolus	Over 1 minute	6.75mg
2	3 hours intravenous loading infusion	24ml/hour	18mg/hour
3	Subsequent intravenous infusion	8ml/hour	6mg/hour

Re-Treatment

In case a re-treatment with TRACTOCILE is needed, it should also commence with a bolus injection of TRACTOCILE 7.5mg/ml, solution for injection followed by infusion with TRACTOCILE 7.5mg/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

- Abruptio placentae
- 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 and Precautions

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 chorioamnionitis.

There is no experience with TRACTOCILE treatment in patients with impaired function of the liver or kidneys (see **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**).

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 ADMINISTRATION**).

In case of intrauterine growth retardation, the decision to continue or reinstate 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 postpartum was not observed during the clinical trials.

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

Effects on ability to drive and use machines

Not applicable.

Adverse 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:

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		

Interactions

It is unlikely that atosiban is involved in cytochrome P450 mediated medicine-medicine 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, 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 TRACTOCILE pharmacokinetics.

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

Overdosage

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.

Pharmaceutical Precautions

List of excipients

Mannitol, hydrochloric acid 1 M and water for injections.

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.

Solution for dilution for infusion

Once the vial has been opened, any 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.

Nature and contents of container

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 discoloration prior to administration.

Preparation of the initial intravenous injection

Withdraw 0.9ml of a 0.9ml labelled vial of TRACTOCILE 7.5mg/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 7.5mg/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 **Incompatibilities**).

Preparation of the intravenous infusion solution

For intravenous infusion, following the bolus dose, TRACTOCILE 7.5mg/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 10ml solution from a 100ml infusion bag and discard. Replace it by 10ml TRACTOCILE 7.5mg/ml concentrate for solution for infusion from two 5ml vials to obtain a concentration of 75mg atosiban in 100ml. The loading infusion is given by infusing 24ml/hour (i.e. 18mg/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 8ml/hour.

Prepare new 100ml 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 (see **Incompatibilities**). 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.

Medicine Classification

Prescription Medicine.

Package Quantities

Solution for injection: 1, 10 vials of 0.9ml

Solution for infusion: 1, 10 vials of 5ml

Further Information

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 20mg/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 foetuses. The exposure of the rat foetus was approximately four times that received by the human foetus 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.

Name and Address

Exclusive New Zealand distributors:

PHARMACO (N.Z.) LTD

P.O. Box 4079

Auckland

Telephone (09) 377-3336

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