1 NAME OF THE MEDICINAL PRODUCT

Atosiban 6.75 mg/0.9 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 0.9 ml solution contains 6.75 mg atosiban (as acetate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution without particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atosiban is indicated to delay imminent pre-term birth in pregnant adult 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%

− a gestational age from 24 until 33 completed weeks

− a normal foetal heart rate

4.2 Posology and method of administration

Posology

Treatment with Atosiban should be initiated and maintained by a physician experienced in the treatment of pre-term labour.

Atosiban is administered intravenously in three successive stages: an initial bolus dose (6.75 mg), performed with Atosiban 6.75 mg/0.9 ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 micrograms/min) of Atosiban 37.5 mg/5 ml concentrate for solution for infusion during three hours, followed by a lower dose of Atosiban 37.5 mg/5 ml concentrate for solution for infusion (subsequent infusion 100 micrograms/min) up to 45 hours. The duration of the treatment should not exceed 48 hours. The total dose given during a full course of Atosiban therapy should preferably not exceed 330.75 mg of atosiban.

Intravenous therapy using the initial bolus injection should be started as soon as possible after diagnosis of pre-term labour. Once the bolus has been injected, proceed with the infusion (See Summary of Product Characteristics of Atosiban 37.5 mg/5 ml, concentrate for solution for infusion). In the case of persistence of uterine contractions during treatment with Atosiban, alternative therapy should be considered.

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

Step	Regimen	Infusion rate	Atosiban dose
1	0.9 ml intravenous bolus injection given over 1 minute	Not applicable	6.75 mg
2	3 hours intravenous loading infusion	24 ml/hour (300 µg/min)	54 mg
3	Up to 45 hours subsequent intravenous infusion	8 ml/hour (100 µg/min)	Up to 270 mg

Re-treatment
In case a re-treatment with atosiban is needed, it should also commence with a bolus injection of Atosiban 6.75 mg/0.9 ml, solution for injection followed by infusion with Atosiban 37.5 mg/5 ml, concentrate for solution for infusion.

Patients with renal or hepatic impairment
There is no experience with atosiban 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.

Paediatric population
The safety and efficacy of Atosiban 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 medicinal product before administration, see section 6.6.

4.3 Contraindications

Atosiban must 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
- 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 placenta

− Any other conditions of the mother or foetus, in which continuation of pregnancy is hazardous

− Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 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. 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).

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 atosiban in these subgroups is therefore uncertain.

Re-treatment with Atosiban is possible, but there is only limited clinical experience available with multiple re-treatments, up to 3 re-treatments (see section 4.2).
In case of intrauterine growth retardation, the decision to continue or reinitiate the administration of Atosiban 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 postpartum bleeding therefore blood loss after delivery should be monitored. However, inadequate uterus contraction postpartum was not observed during the clinical trials.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Atosiban should only be used when pre-term labour has been diagnosed between 24 and 33 completed weeks of gestation. If during pregnancy the woman is already breast-feeding an earlier child, then breast-feeding should be discontinued during treatment with Atosiban, since the release of oxytocin during breast-feeding may augment uterine contractility, and may counteract the effect of tocolytic therapy.

Breastfeeding

In atosiban clinical trials no effects were observed on breast-feeding. Small amounts of atosiban have been

shown to pass from plasma into the breast milk of breast-feeding women.

Fertility

Embryo-fetal toxicity studies have not shown toxic effects of atosiban. No studies were performed that covered fertility and early embryonic development (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Possible adverse reactions of atosiban were described for the mother during the use of atosiban in clinical trials. In total 48% of the patients treated with atosiban experienced adverse reactions during the clinical trials. The observed adverse reactions were generally of a mild severity. The most commonly reported adverse reaction in the mother is nausea (14 %).

For the newborn, the clinical trials did not reveal any specific adverse reactions of atosiban. The infant adverse reactions 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.

MedDRA System Organ Class (SOC)	**Very common**	**Common**	**Uncommon**	**Rare**
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders		Hyperglycaemia		

Psychiatric disorder			Insomnia	
Nervous system disorders		Headache Dizziness		
Cardiac disorders		Tachycardia		
Vascular disorders		Hypotension Hot flush		
Gastrointestinal disorders	Nausea	Vomiting		
Skin and subcutaneous tissue disorders			Pruritis Rash	
Reproductive system and breast disorder				Uterine haemorrhage Uterine atony
General disorders and administration site conditions		Injection site reaction	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 post-marketing.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the yellow card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynecologicals, ATC code: G02CX01

Mechanism of action

Atosiban 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.

Pharmacodynamic effects

In human pre-term 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 pre-term labour at 23–33 weeks of gestation and were randomised to receive either atosiban (according to this labelling) or β-agonist (dose-titrated).

Clinical efficacy and safety

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 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 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 2491 (813) grams in the atosiban group and 2461 (831) grams in the β-agonist group (p=0.58).

Fetal and maternal outcome did apparently not 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 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 4.4).

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 4.3).

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 with 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 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 atosiban group).

5.2 Pharmacokinetic properties

Absorption
In healthy non-pregnant subjects receiving atosiban infusions (10 to 300 micrograms/min over 12 hours), the steady state plasma concentrations increased proportionally to the dose.

Distribution
The clearance, volume of distribution and half-life were found to be independent of the dose.

In women in pre-term labour receiving atosiban by infusion (300 micrograms/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 litres/h. Mean value of volume of distribution was 18.3 ± 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 fetal compartments differs substantially. Atosiban does not partition into red blood cells.

Atosiban passes the placenta. Following an infusion of 300 micrograms/min in healthy pregnant women at term, the fetal/maternal atosiban concentration ratio was 0.12.

Biotransformation
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. 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 4.6).

Elimination
There is no experience with atosiban 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 4.4).

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

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Hydrochloric acid concentrated

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

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

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

Type I glass ampoule 2 ml.

Glass ampoule (7.5 mg/ml): pack of 1x 2ml

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

Preparation of the initial intravenous injection

Withdraw 0.9 ml of a 0.9 ml labelled ampoule of Atosiban 6.75 mg/0.9 ml, solution for injection and administer slowly as an intravenous bolus dose over one minute, under adequate medical supervision in an obstetric unit.

Atosiban 6.75 mg/0.9 ml, solution for injection should be used immediately, after the ampoule has been opened.

7 MARKETING AUTHORISATION HOLDER

Ibigen Srl,
via Fossignano 2,
04011 Aprilia (LT)
Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 31745/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/05/2022

10 DATE OF REVISION OF THE TEXT

31/05/2022