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**UK Medicines Information Pharmacists Group**

**NEW MEDICINES ON THE MARKET**

**Evaluated information for the NHS**

**ATOSIBAN**

**Summary**

- Atosiban, a synthetic peptide, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has been developed as a new tocolytic therapy in the treatment of preterm labour.
- Atosiban may be marginally less effective in the management of preterm labour than the beta<sub>2</sub>-agonists (ritodrine, terbutaline, and salbutamol) currently used as tocolytics. In clinical studies, more patients initially randomised to atosiban required an alternative tocolytic due to insufficient efficacy than those initially randomised to a beta<sub>2</sub>-agonist.
- However, atosiban is significantly better tolerated than the beta<sub>2</sub>-agonists, particularly with regard to the cardiovascular side effects. In clinical studies, significantly more patients initially randomised to beta<sub>2</sub>-agonists required an alternative tocolytic due to adverse effects (mainly cardiovascular) than those patients initially randomised to atosiban.
- Atosiban may be a useful alternative for those patients with preterm labour who cannot tolerate beta<sub>2</sub>-agonists due to adverse effects.
- Atosiban is considerably more expensive than the beta<sub>2</sub>-agonists.

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## ATOSIBAN

<b>APPROVED NAME:</b>	Atosiban
<b>BRAND NAME (MANUFACTURER):</b>	Tractocile (Ferring Pharmaceuticals Ltd)
<b>PRESENTATION:</b>	0.9ml vial containing atosiban 7.5mg/ml solution for injection. 5ml vial containing atosiban 7.5mg/ml concentrate for solution for infusion.
<b>BNF THERAPEUTIC CLASS</b>	BNF 7.1.3 Myometrial relaxants
<b>LICENSED INDICATIONS</b>	To delay imminent preterm birth in pregnant women aged $\geq$ 18 years with regular uterine contractions of at least 30 seconds duration at a rate of $\geq$ 4 per 30 minutes, with cervical dilation of 1-3cm (0-3 for nulliparas) and effacement of $\geq$ 50%, a gestational age from 24 until 33 completed weeks and a normal fetal heart rate.
<b>DOSAGE AND ADMINISTRATION</b>	The initial bolus dose of 6.75 mg atosiban is given intravenously over 1 minute, followed by a continuous intravenous infusion of 300 micrograms per minute for 3 hours. This is followed by an intravenous infusion of 100 micrograms per minute for up to a maximum 45 hours. The maximum duration of treatment is 48 hours and the maximum dose is 330mg atosiban.
<b>THERAPEUTIC COMMENT</b>	Atosiban is an oxytocin antagonist, a new class of tocolytic, licensed for the management of preterm labour. It may be marginally less effective than $\beta$ 2 agonists, but is better tolerated and less likely to cause cardiovascular side effects.
<b>SECTOR OF USE</b>	Hospital [Y] Primary Care [N]
<b>COST AND COURSE DETAILS</b>	(MIMS November 2000) 0.9 ml 7.5mg/ml solution for injection - £20.00 5 ml 7.5mg/ml concentrate for solution for infusion - £55.00 Maximum treatment cost = £515.00
<b>TREATMENT ALTERNATIVES</b>	beta <sub>2</sub> -agonists e.g. ritodrine, terbutaline, and salbutamol.

Tocolytic agent	Treatment regimen	Cost
Ritodrine	Initially 50 mcg/min increased by 50 mcg every 10 mins until a max of 350 mcg/min for 48 hours.	£42.90
Terbutaline	Initially 5 mcg/min for 20 mins, increasing by 2.5 mcg/min at 20 min intervals until contractions stop to a max 20 mcg/min. Followed by 5 mg tds orally for 48 hrs.	£1.22
Salbutamol	Initially 10 mcg/min increased by 5 mcg/min every 10 min to max 45 mcg/min for 1 hour then reduced by 50% every 6 hours. Followed by 4 mg tds orally for 24 hrs.	£11.50

## INTRODUCTION

Atosiban, a synthetic peptide, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has been developed as a new tocolytic therapy in the treatment of preterm labour.

Preterm labour is a major cause of perinatal mortality and morbidity. Infants delivered prematurely (before 37 weeks gestation) have incompletely developed homeostatic mechanisms, leaving them susceptible to potentially life threatening complications such as respiratory distress syndrome, infection, jaundice, hypothermia and hypoglycaemia [1].

Despite steady improvements in neonatal survival and morbidity rates over recent years, primarily as a result of improved neonatal care, there has been little reduction in the incidence of preterm birth [2]. In the UK, the incidence of preterm delivery is about 7% [1].

Pharmacological inhibition of uterine contractility (tocolysis) to postpone delivery is the current mainstay of management of preterm labour. Tocolytics can delay delivery long enough for the mother to be administered corticosteroids to encourage fetal lung maturation or to allow transfer to a specialist tertiary centre. Most frequently, beta<sub>2</sub>-agonists such as ritodrine, terbutaline and salbutamol are used. Other tocolytics include indomethacin, calcium channel blockers and magnesium sulphate. Atosiban is an oxytocin antagonist and represents a novel tocolytic agent [1].

## PHARMACOLOGY

Oxytocin is believed to initiate uterine contractility by increasing the intracellular calcium concentration of myometrial cells through a direct effect on membrane bound oxytocin receptors. Oxytocin further stimulates uterine contractility and initiates cervical ripening by stimulating the release of prostaglandins in the decidual and fetal membranes [3].

Atosiban is a synthetic peptide which is a competitive antagonist of human oxytocin at receptor level in the uterus, and potentially also in the decidual and fetal membranes. Administration results in a dose-dependent inhibition of uterine contractility, and studies have shown a reduction in oxytocin-mediated prostaglandin release. The onset of uterine relaxation is rapid with contractions being significantly reduced within 10 minutes [4].

## PHARMACOKINETICS

In women with preterm labour receiving atosiban (300 mcg/min for 6-12 hours) steady state plasma concentrations were reached within an hour following the start of infusion (mean 442 ± 73ng/ml, range 298 to 533ng/ml). Atosiban clearance, volume of distribution and half-life were found to be independent of the dose [4].

Atosiban is 46-48% plasma protein bound in pregnant women. It crosses the placenta, a dose of 300 mcg/min administered to healthy pregnant women at term produced a fetal/maternal atosiban concentration ratio of 0.12 [4].

Atosiban is metabolised to two metabolites (M1 and M3), the main one, M1 being as potent as the parent compound in inhibiting oxytocin-induced contractions in vitro [4]. The ratios of M1 to atosiban concentrations in plasma were 1.4 at the second hour and 2.8 at the end of the infusion. The urinary concentration of atosiban is around 50 times lower than that of M1. M1 is excreted in breast milk [4].

Plasma concentrations rapidly decline with an initial ( $t_{\alpha}$ ) and terminal ( $t_{\beta}$ ) half-life of 0.21 ± 0.01 and 1.7 ± 0.3 hours, respectively. Mean clearance was 41.8 ± 8.2 l/hr and mean volume of distribution was 18.3 ± 6.8 L [4].

There is no experience with atosiban in patients with impaired liver or kidney function [4].

## EFFICACY

### Pivotal Studies

Atosiban has been compared with the beta<sub>2</sub>-agonists ritodrine, salbutamol and terbutaline in three separate double blind studies [5-7], only one of which is published in full [5]. The three studies were of a similar design and a pooled analysis of the results was planned from the outset [8]. All studies included women with preterm labour diagnosed by the presence of regular uterine contractions of at least 30 seconds duration at a rate of  $\geq 4$  per 30 mins, cervical dilation of 1-3 cm (0-3 cm for nulliparus) and effacement of  $\geq 50\%$ . Patients were aged 18 or over at a gestation of 23-33 weeks carrying 1-2 normal fetus. The atosiban dose and regimen was identical to its license specification. Regimens for the beta<sub>2</sub>-agonists are given in the table [table 2].

The primary efficacy endpoint was the proportion of women who did not experience treatment failure (TF) at 7 days where TF was defined as either the need for an alternative tocolytic agent or delivery. The reasons for an alternative tocolytic could include either lack of efficacy or tolerability to the initial agent [8].

The results for the individual studies can be seen in table 2 [5-7]. The pooled results of the intent to treat analysis showed that the proportion of women with TF > 7 days was higher in the atosiban than the beta<sub>2</sub>-agonist group (60% vs. 47.7%, respectively  $p = 0.002$ ) [8]. Similarly the TF > 48 hours was higher in the atosiban group than the beta<sub>2</sub>-agonist group (74.5% vs. 69.3%, respectively,  $p = 0.038$ ). However, discontinuation of the assigned treatment due to insufficient efficacy was more frequent in the atosiban group than the beta<sub>2</sub>-agonist group (14% vs. 6%, respectively) [8]. Conversely, discontinuation of the assigned treatment due to adverse effects was more frequent in the beta<sub>2</sub>-agonist group than in the atosiban group (10.7-29.8% vs. 0.8-1.7%) [5-7]. Thus, atosiban may be less effective than beta<sub>2</sub>-agonists, but appears to be better tolerated.

No significant differences were observed in the pooled analysis for mean gestational age at delivery or in fetal or infant main outcome parameters (birth weight, survival, frequency of respiratory distress syndrome or intracranial haemorrhage) [8].

### Other Studies

In a randomised controlled study atosiban was more effective than placebo in treating preterm labour [9]. However, this study showed imbalance at randomisation, through differences in gestational age at inclusion and in the severity of the preterm labour [8].

A continuous infusion of atosiban (30 mcg/min) was more effective than placebo for maintenance therapy in 251 women who had previously responded to atosiban for preterm labour [10].

In a controlled study a 2-hour infusion of atosiban was more effective than placebo in reducing uterine contractility in 121 women with preterm labour [11].

## PROMOTIONAL DATA

The promotional leaflet for atosiban pictures a pregnant lady, with the key message underneath reading "The tocolytic with two lives in mind". The following claims are made

- Rapid onset of action
- Sustained inhibition of uterine contractility
- Side effect incidence comparable to that of placebo
- Effective in delaying preterm labour

It has been promoted as a novel tocolytic with a better maternal safety profile than beta-agonists. Atosiban does appear to have a better safety profile than the selected beta<sub>2</sub>-agonists it has been compared to. However it may be marginally less effective than these agents. Overall adverse effects are more common with atosiban compared with placebo.

## ADVERSE EFFECTS (see SPC)

Table 1. Maternal adverse effects [8]:

Frequency (%)	Atosiban (n=1260)	Beta <sub>2</sub> -agonists (n=372)	Placebo (n=251)
Nausea	13.9	15.9	5.6
Headache	9.3	18.5	7.6
Dizziness	2.6	1.9	0.8
Tachycardia	2.5	75.5	1.2
U.T.I.	2.3	4.8	0.4

In addition, fetal tachycardia was more common in patients receiving beta<sub>2</sub>-agonists than those receiving atosiban (26.3% vs. 0.9%) [8].

## CONTRAINDICATIONS/ PRECAUTIONS (See SPC)

Atosiban should not be administered to pregnant women with any of the following conditions:

- Gestational age below 24 or over 33 completed weeks.
- Premature rupture of the membranes at >30 weeks of gestation
- Intrauterine growth retardation
- 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 or abruptio placenta
- Any other conditions of the mother, or fetus, where continuation of pregnancy is hazardous.
- Any known hypersensitivity to the active substance or any of the excipients.

There is only limited experience in the use of atosiban in multiple pregnancies or in the gestational age group between 24 and 27 weeks.

Although retreatment with atosiban is possible, there is only limited clinical experience with up to 3 retreatments

No interaction studies have been performed.

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**Table 2. Clinical Studies with atosiban**

Ref	Design	Drug Treatments	Type of patients	Response measures	Results		P value	Comments	
					atosiban	placebo			
[9]	R, DB, PC, MC.	Atosiban (n=246) 6.75 mg bolus over 1 minute then 300 µg/min for 3 hours and 100 µg/min for up to 45 hours.  Placebo (n=255).	Women with PTL between 20 and 33 weeks 6 days gestation, with intact membranes and cervical dilatation of ≤3cm.	1 <sup>o</sup> endpoint =Time from the start of the study drug to delivery (TTD) or therapeutic failure requiring an alternative agent. 2 <sup>o</sup> endpoint= Proportion of patients that remained undelivered (ND) and did not receive an alternative tocolytic (NA) after 24h, 48h and 7day.				This study was characterised by an imbalance at randomisation, and therefore results should be interpreted cautiously.	
					TTD median/ range	25.6 days (0-115.5)	21.0 days (0-110.7)		p=0.6
					ND+ NA at 24 hours	73%	58%		p<0.001
					ND+ NA at 48 hours	67%	56%		p=0.008
				ND+ NA at 7 days	62%	49%	p=0.003		
[10]	R, DB, PC, MC	Maintenance treatment with atosiban (n=261) 30 µg/min to the end of 36 weeks gestation.  Placebo (n=251).	Women between 20 and 33 weeks 6 days gestation, with intact membranes, who had previously responded to atosiban for PTL.	1 <sup>o</sup> endpoint = the number of days from the start of maintenance therapy until the first recurrence of labour.  2 <sup>o</sup> endpoint = % patients requiring subsequent i.v. atosiban therapy.				Initial treatment with atosiban was not randomised or placebo controlled. Atosiban has not been licensed for maintenance therapy.	
					1 <sup>st</sup> recurrence (median)	32.6 days	27.6 days		p=0.02
					Subs. i.v. atosiban	23%	31%	p=NS	
[5]	R, DB, MC	Atosiban (n=128) 6.75mg i.v. bolus, 300 µg/min for 3 hours, then 100 µg/min for up to 18 hours. Ritodrine (n=124) 0.10-0.35 mg/min i.v. for up to 18 hours.	Women with PTL between 23 and 33 gestational weeks, with intact membranes.	Number of women who had not experienced treatment failure (TF) after 48 hours and after 7 days.				More women on atosiban discontinued due to a lack of efficacy (20.6% vs. 4.1%) More women discontinued ritodrine due to adverse events (29.8% vs. 0.8%).	
					No TF at 48h	71.4%	66.9%	p=0.29	
					No TF at 7 days	64.3%	52.9%	p=0.03	
[6&8]	R, DB, MC	Atosiban (n=116) i.v. bolus of 6.75mg, then 300 µg/min for 3 hours and 100 µg/min for up to 18 hours.  Terbutaline (n=129) 5-20 µg/min i.v. for up to 18 hours.	Women with preterm labour, between 23 and 33 gestational weeks.	Number of women who had not experienced treatment failure (TF) after 48 hours and after 7 days.				More women discontinued atosiban due to a lack of efficacy (9% vs. 5%). More women receiving terbutaline discontinued as a result of adverse effects (13.2% vs. 1.7%).	
					No TF at 48h	72.2%	68.2%	p=0.52	
					No TF at 7 days	55.6%	43.4%	p=0.08	
[7&8]	R, DB, MC	Atosiban (n=107) i.v. bolus of 6.75 mg, then 300 µg/min for 3 hours and 100 µg/min for up to 48 hours.  Salbutamol 2.5-45 µg/min by i.v. infusion for up to 48 hours.	Women with preterm labour, between 23 and 33 gestational weeks.	Number of women who had not experienced treatment failure (TF) after 48 hours and after 7 days.				More women discontinued atosiban due to lack of efficacy (13% vs. 6%). More women discontinued salbutamol due to adverse events (10.7% vs. 0.8%).	
					No TF at 48h	79.8%	75.2%	p=0.15	
					No TF at 7 days	58.8%	46.3%	p=0.02	

MC Multi-centre PTL Pre-Term Labour R Randomised TTD Time to Delivery DB Double Blind  
 TF Treatment Failure (defined as delivery or the need for an alternative tocolytic) PC Placebo Controlled NS Not Specified