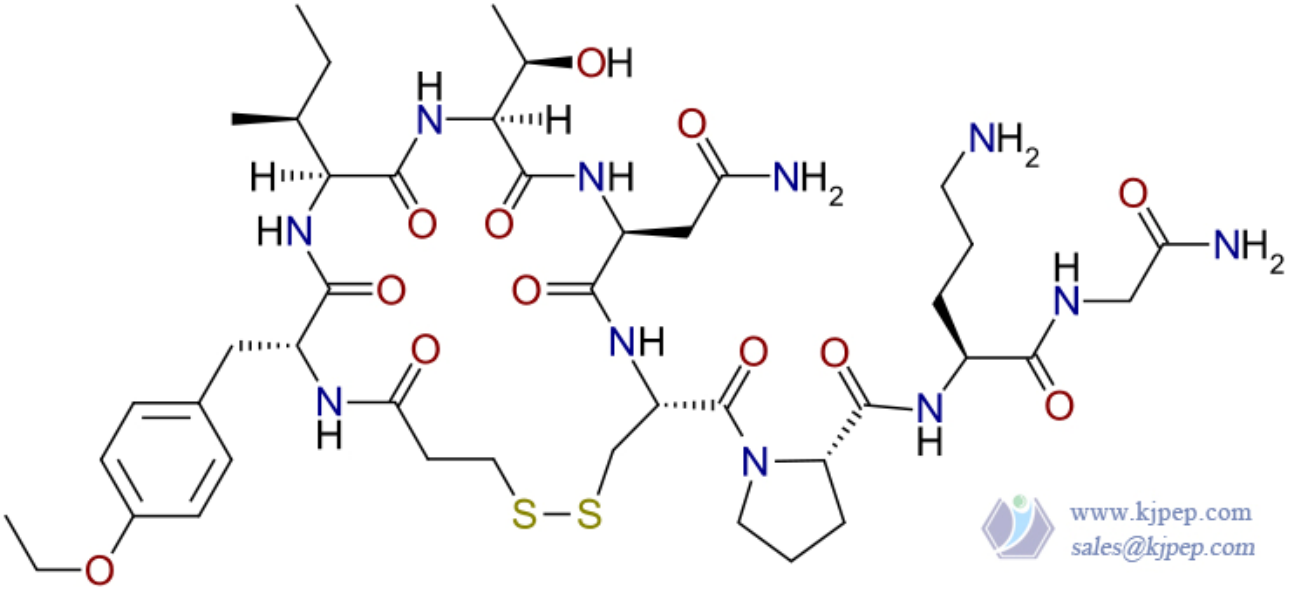
Chengdu KaiJie Biopharm Co., Ltd.
Segment 1, Industrial Road, Dayi county, Chengdu, Sichuan, P. R. China，611330
Tel： 86-28-88208155，Fax： 86-28-88203632 WEB: www.kjpep.com

About Author

Chengdu Kaijie Biopharm Co, Ltd. (KJBP) is one of leading peptide manufacturers in Asia. With its highest capacity of production in China and the outstanding quality of peptide products, Kaijie holds a unique position.

Atosiban



1. 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 beta2-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 randomized to a beta2-agonist.

However, atosiban is significantly better tolerated than the beta2-agonists, particularly with regard to the cardiovascular side effects. In clinical studies, significantly more patients initially randomized to beta2-agonists required an alternative tocolytic due to adverse effects (mainly cardiovascular) than those patients initially randomized to atosiban.

Atosiban may be a useful alternative for those patients with preterm labour who cannot tolerate beta2-agonists due to adverse effects.

Atosiban is considerably more expensive than the beta2-agonists.

- CAS No. 90779-69-4
- ATC Code. G02CX01
- PubChem CID 68613
- Formula $\mathbf{C_{43}H_{67}N_{11}O_{12}S_2}$
- Mol.Mass 994.199

2. Adult Dosage

Preterm labor

a) Optimal doses have not been established. **Atosiban** is given via a continuous intravenous infusion. An initial intravenous bolus is recommended to shorten the time to cessation of uterine contractions. For women with preterm labor and intact membranes, an effective intravenous (IV) dosing regimen has begun with a 6.75 milligram bolus, followed immediately by infusion of 300 micrograms/minute for 3 hours and then a 100 micrograms/minute infusion

b) A bolus dose of 2 milligrams (mg), followed by infusion of 100 micrograms (mcg)/minute has been effective. **Atosiban** was continued 6 hours after the last contraction (last contraction preceding one hour of no contractions) to a maximum of 12 hours. A higher bolus/infusion rate (6 mg/300 mcg/minute) was not more effective.

c) In women with preterm labor and intact membranes who achieve uterine quiescence with intravenous **atosiban**, maintenance therapy of 30 micrograms/minute administered by a continuous subcutaneous infusion pump may prolong uterine quiescence

2.0 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.

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. 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. 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. Plasma concentrations rapidly decline with an initial (ta) and terminal (tb) 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. There is no

experience with atosiban in patients with impaired liver or kidney function.

2.1 Onset and Duration

Onset

1) Initial Response

PRETERM LABOR, INTRAVEOUS INFUSION: A decline (not cessation) in uterine activity has occurred within 60 minutes of initiation of a 300-mcg/minute infusion (no preceding bolus)

2) Peak Response

PRETERM LABOR, INTRAVEOUS: Cessation of uterine contractions has occurred in about a fourth of patients within 2 hours of initiation of an intravenous bolus/continuous infusion regimen (2 or 6 mg followed by 100 or 300 mcg/minute). Without an initial bolus dose, control of uterine activity is somewhat slower

2.2 Drug Concentration Levels

Time to Peak Concentration

INTRAVENOUS INFUSION: within 60 minutes

Mean steady-state plasma concentrations of 442 ng / mL were achieved within one hour of initiation of a 300-mcg/minute infusion (no initial bolus). After infusion discontinuation, plasma levels declined to less than 10 ng/mL after 4 hours (Goodwin et al, 1995). Data for bolus/infusion regimens are lacking.

CONTRAINDICATIONS/ PRECAUTIONS:

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.