SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Tractocile. For information on changes after approval please refer to module 8.

1. Introduction

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

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 300µg/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.

Tractocile is a new medicinal product, developed by Ferring AB in collaboration with the R.W. Johnson Pharmaceuticals Research Institute. It contains atosiban, a synthetic peptide acting as an oxytocin antagonist. Tractocile is intended for the treatment of pre-term labour (PTL).

Pre-term birth (i.e. birth before 37 weeks) is a common obstetric condition, occurring in 10-15 percent of all births; it is associated with an increased risk of neonatal death and congenital neurological disability, including cerebral palsy. Although the common definition of pre-term birth includes all births before 37 weeks of gestation, births before 32 weeks (about 2% of all births) are responsible for most neonatal deaths and pathologies.

Beta-mimetic agents are currently widely used in the treatment of pre-term labour. Data from randomised trials have suggested that beta-mimetic agents prolong pregnancy for up to 48 hours. Nevertheless, there is a high rate of major adverse events such as tachycardia (frequent), pulmonary oedema, myocardial ischemia (rare) or metabolic changes. Other non-utero-specific agents as magnesium sulphate, calcium channel blockers and non-steroidal anti-inflammatory drugs have been used for tocolysis.

Atosiban inhibits the action of oxytocin; this hormone mobilises calcium in myometrial cells and starts uterine contractions. Using a different mechanism of action, atosiban provides a new approach to the treatment of pre-term labour.

Atosiban is subject to restricted medical prescription: ”Hospital use only”.

2. Chemical, pharmaceutical and biological aspects

Composition

Formulation of Tractocile:

- the active substance atosiban is present as an acetate salt (the substance contains also water, acetic acid and ethanol) corresponding to 7.5 mg/ml of atosiban free base,
- Mannitol -isotonicity agent- (50 mg/ml),
- pH is adjusted to 4.5 with 1 M hydrochloric acid,
- water for injections (to 1 ml).

The composition used in the clinical trials is identical with the one proposed for marketing.

Tractocile is available in two pharmaceutical forms:

- Solution for injection for intravenous use 7,5 mg/ml, in a vial of 0,9 ml (bolus injection),
- Concentrate for solution for infusion for intravenous use, in a vial of 5 ml (i.v. infusion).

Primary packaging:

Clear, borosilicated, type I, colourless glass vials, sealed with grey, siliconised bromobutyl rubber stopper, type I, and flip-off cap of polypropylene and aluminium.

Active substance

Atosiban is a chemically-synthesised nonapeptide of the following formula [Mpa^{1},D-$Tyr(Et)^{2}$,Thr^{4}, Orn^{8}] oxytocin.

The active substance atosiban employed for the most of the batches used in preclinical and clinical studies was obtained by solid phase peptide synthesis (SPPS) and after 1994 by liquid phase peptide synthesis (LPPS) followed by a more efficient purification process. The impurity profiles obtained with the two methods have been shown to be similar. However, the impurity level obtained with the LPPS is lower. Thereby, the difference in manufacture of the active substance is considered of no clinical importance.

The starting materials are amino-acid derivates, solvents and other reagents.

Protected peptide fragments are synthesised by Boc-chemistry, to yield a linear nonapeptide, followed by deprotection by reduction with sodium in liquid ammonia and by disulphide formation by iodine oxidation. The final purification involves dilution in ethanol and purification by ion exchange chromatography (cation) and reverse phase chromatography. Finally the active substance is concentrated by reversed osmosis and thereafter lyophilised. The synthesis has been sufficiently validated with 4 batches of 2 kg atosiban acetate.

The atosiban molecule contains nine chiral centres. The amino acid residues of tyrosine, aspargine, cyteine, proline and ornithine have one asymmetrical carbon each and the residues of isoleucine and threonine have two each. All of them are in the L-form, except for tyrosine, which is in the D-form. The D-form respectively the L-form have not been found in production batches in levels above 0.1%. Eleven diastereomers with one chiral centre can potentially be present in the raw material or formed during the synthesis of atosiban. However, neither of the epimers have been found in concentration above 0.1%. Cis-trans isomerisation occurs at the Ys-Pro bond. The *trans* form is the major form

Atosiban is a white to off-white, very hygroscopic, freeze-dried amorphous powder, which is soluble in water, acetic acid, 0.1 M ammonium acetate, pH 6.0 and 6.8, methanol, ethanol and dimethylformamide.

More than 32 impurities have been observed. 17 of these have been observed at and above 0.1%. The structure of these impurities has been established by Mass Spectrometry and Nuclear Magnetic Resonance. However, in the full production batches synthesised by the liquid phase peptide route the content of impurities is lower. Therefore only specific limits on 9 impurities have been set and in addition a limit on = 0.1% for other single impurities. Total impurities have been set at a maximum of 3%.

Through studies of general toxicity, reproduction, mutagenicity, carcinogenicity, the safety of the main synthetic impurities and of the degradation products in atosiban has been evaluated, and the specified limits have been validated on the basis of these studies.

The active substance contains low or negligible amounts of the residual solvent except for ethanol and acetic acid.

The results of batch analysis, including three large scale batches, show good conformity with the proposed specification when tested by validated methods.

Stability: Three batches synthesised by LPPS have been stored in 30 ml HDPE bottles at different conditions.

The parameters tested were peptide content, peptide purity, specific optical rotation, water content, acetic acid/acetate content and appearance.

At -20°C and at refrigerator conditions the active substance is relatively stable. At room temperature and specially when exposed to light severe degradation does occur. At real time condition, the total content of impurities increases maximal about 0.6%.

A retest period of 12 months when stored below 8°C and protected from light is suggested until further results are available.

Other ingredients

Mannitol complies with the USP and Ph.Eur. specification (harmonisation between the two monographs, and also with that of the Japanese Ph., is ongoing).

Water for injections is controlled according to Ph.Eur.

Product development and finished product

The choice of the auxiliary substance, *i.e.*, mannitol, confirmed by compatibility studies, was originally considered suitable for the freeze drying process. Stability data of the isotonic solution (osmolarity value 310 mOsm/kg) showed that the Atosiban injection was stable at 5°C for 2 years.

For manufacture, mannitol is dissolved in water for injection. Atosiban is added to the mannitol solution and pH is adjusted with hydrochloric acid. The bulk solution is then diluted to final volume with water for injection and double sterile filtered (0.22 μm), aseptically filled and sealed.

Before filling, the vials are rinsed with water for injection and sterilised and depyrogenised by hot air in a process shown to achieve an endotoxine reduction of at least 3 log.

The rubber stoppers are rinsed with water for injection with silicone oil added. After rinsing, the stoppers are packed in autoclave plastic bags and steam sterilised (121°C, thermal Fo=20). A compatibility study of the rubber stopper and the finished product has been presented. Calcium, zinc, and aluminium content were determined on batches stored up to 39 months at 5 and 30°C. Levels below 1.9 ppm were observed.

The compounding and the filling processes are performed in accordance with the GMP.

The validation of the manufacturing process includes 5 batches of 50 litre each. Three of the batches contain atosiban synthesised by the solid phase route and two of the batches atosiban synthesised by the liquid phase route. The manufacturing procedure has been shown to be reproducible.

Specifications: The requirements are considered adequate to control the finished product. The limits on atosiban are 93-107%. The company proposes these limits in stead of ± 5% because the active is hygroscopic and electrostatic properties make it difficult to handle. The limits on degradation products are increased compared to the active substance. However, these are supported by toxicology studies. The total sum of degradation products is set at 1.7 %. The limits for the volume are 0.9-1.2 ml for 0.9 ml declared volume and 5.0-5.6 ml for 5 ml declared volume. The endotoxin test (limit 12.2 EU/mg atosiban) is performed according to the Ph.Eur. method (gel clot method).

Results from 24 batches have been presented including two batches manufactured with atosiban synthesised with the liquid phase peptide route (production batch size). The results have shown that the process is reproducible and the Atosiban solution meets the determined specifications.

Stability of the finished product: The data generated by five 50 l batches of atosiban injection support a minimum 24 month expiry dating if the product is stored at 2-8°C, protected from light. Parameters investigated were assay, degradation products, appearance, particular matter, pH.

The limits for peptide content are 93-107 % at the release and 90-107 % at the shelf life. The limits for the sum of the related substances (excluding CAP2, CAP3, CAP5 and CAP26) are 1.5 % at the release and 1.7 % at the shelf life. In the specification for the degradation products, CAP4, CAP7, CAP8 and CAP44 are included.

The stability of the active ingredient and of the finished product is well documented: the studies support their proposed shelf life and storage conditions as defined in the SPC.

The compatibility of atosiban with 3 fluids for infusion (5% glucose, Normal saline, Lactated Ringer) has been investigated. The compatibility study showed that the solutions were chemically stable for 96 hours and the proposed shelf life of 24 hours is supported.

Discussion on chemical, pharmaceutical and biological aspects

The chemical and pharmaceutical documentation is in general satisfactory. The study of the peptide related substances is comprehensive. The result of the synthesis and the purification processes for atosiban drug substance gives a substance, which reproducibly meets the quality specification. The manufacturing process of the finished product is in compliance with GMP.

Some additional confirmation and clarification of minor quality issues are requested as Follow-up Measures.

3. Toxico-pharmacological aspects

Atosiban is a synthetic peptide, an oxytocin analogue, designed to inhibit uterine contractions before the normal term of pregnancy by acting on oxytocin receptors.

Pharmacodynamics

In vitro studies

Receptor binding:

Arginine-vasopressin (AVP) and oxytocin (OT) receptors are distinct, though structurally related, gene products belonging to the family of G protein-coupled receptors. They are classified as follows on the basis of their order of potency (AVP>OT for AVP receptors and OT≥VP for OT receptors):

- AVP-V_1 vasopressin receptors, coupled to Gq/11 protein, mediate the contractile effects of AVP on vascular smooth muscle and its glycogenolytic response in the liver. V_{1A} receptor mediates the vasopressor effect.
- AVP-V_2 vasopressin receptors, coupled to Gs protein, mediate the antidiuretic effect.
- OT, oxytocin receptor, coupled to Gq/11 protein, mediate uterine contractions and contractions of myoepithelial cells surrounding mammary alveoli which lead to milk ejection.

Atosiban has been tested *in vitro* for its affinity on AVP/OT receptors using uterine preparations from different animal species, including humans. The overall results clearly demonstrate that atosiban is a high-affinity, competitive antagonist, both for OT and AVP receptors.

The selectivity of atosiban for other peptide or transmitter receptors has been investigated firstly for α1-adrenergic, 5-HT1A and 5-HT2 receptors, and then with a broad receptor screening study. Atosiban has little or no affinity for the receptors studied.

Atosiban gives an appreciable concentration of metabolite M1. An *in vitro* study using human myometrial tissue strips showed that M1 has the same activity as atosiban, since pA2 are not statistically different.

Pharmacological activity *in vitro*:

The antagonistic activity of atosiban has been documented *in vitro* in isolated tissues from different species, including humans. It appears that atosiban is a competitive antagonist of OT and AVP effects on uterine contractility. A quantitative comparison of the potency of atosiban on OT and AVP receptors is not always possible, since in many experiments the relative pA_2 values have not been calculated.

Atosiban did not modify the basal contractility of the myometrium or angiotensin I and II and $PGF_{2\alpha}$-induced uterine activity.

In vivo studies

The effect of atosiban on labour has been evaluated *in vivo* in two animal species: rat and kangaroo. Atosiban, given subcutaneously every 5 minutes for 1 hour after the first pup delayed the birth of the second pup in a dose-dependant fashion. Continuous i.v. infusion of atosiban (50 µg/kg/min) delayed the birth by approximately 1 hour beyond that observed in the vehicle control group. In the kangaroo, an infusion of atosiban 3 to 7 days before delivery also increased the duration of gestation without effect on the viability and weight of the pups.

General and safety pharmacology programme

Behaviour and pain studies in rats and mice did not indicate that atosiban has any important action on CNS and autonomic system activity.

Safety pharmacology studies in rats, ewes, dogs and monkey show that the cardiovascular and pulmonary effects of atosiban are limited and probably without clinical importance. Atosiban did not influence cardiopulmonary parameters in pregnant and non-pregnant animals but antagonised vasopressin's effect on the vascular system. The inhibitory potency of atosiban on the OT-stimulated uterus is about 40 times its antivasopressor activity.

Atosiban seems to antagonise the renal effects of oxytocin more than those of vasopressin. The drug significantly increased urine elimination in overhydrated animals but did not antagonise the antidiuretic activity of vasopressine. Atosiban neither changed sodium excretion in unilaterally nephrectomised rats, nor antagonized vasopressin action, but reversed OT-induced natriuresis. However, these results in particular models (overhydrated or partially nephrectomized rats) do not suggest a major toxicological impact of atosiban in individuals with normal renal function.

At a dose (0.1 µg/kg) much lower than needed to inhibit OT-induced uterine contractions in female rats atosiban significantly lowered plasma corticosterone levels in male rats. Blood glucose levels decreased and insulin rose after atosiban in female rats, while the drug did not influence the increase of insulin caused by OT (2 ng/kg).

Atosiban had no effects on non-uterine smooth muscle.

Pharmacodynamic drug interactions

The inhibitory effect of atosiban on *in vitro* myometrial contraction is potentiated by terbutaline and not affected by indomethacin. No *in vivo* interaction studies have been carried out.

Comparative effect between SPPS and LPPS atosiban

Most preclinical studies have been performed with atosiban prepared by a solid phase peptide synthesis (SPPS) which is a different route of synthesis compared to a liquid phase peptide synthesis (LPPS) proposed for marketing. In support, the applicant has performed bridging preclinical studies.

The two methods have been compared in vitro on oxytocin-induced contractions of rat uterine strips and human myometrial tissue, but no studies have been done in vitro to test the potency of LPPS atosiban on vasopressin receptors. The two preparations have never been directly compared in experiments on human tissues; indirect comparisons suggest there is no real difference with regard to inhibition of the OT effect on human tissue, but direct comparisons on animal tissue suggest potential difference.

Summary of salient findings

The pharmacodynamic profile of atosiban supports the proposed use for inhibiting pre-term labour: Atosiban is a high-affinity, competitive, though non-selective, antagonist of oxytocin receptors. Atosiban shows similar affinity for arginine-vasopressin (AVP) receptors. All important functional system have been investigated, and no atosiban-induced effects that could cause safety concerns for the proposed human use have been identified.

However the relative antagonistic potency of the LPPS preparation and the SPPS preparation on OT and AVP was not adequately assessed.

Pharmacokinetics

Pharmacokinetic studies of atosiban have been carried out in rats, rabbits, dogs, monkeys and ewes. The concentrations of atosiban were determined by validated RIA methods. In some studies radiolabelled atosiban (labelled on the phenyl nucleus of tyrosine) was employed. Several of them were conducted according to Good Laboratory Practice. No pharmacokinetic studies have been done with oral atosiban since the drug was designed for parenteral use.

Absorption of atosiban after subcutaneous (s.c.) dosing is fast (≤ 30 min) in all species tested (female rats, rabbits and dogs). The exposure to the drug after s.c. and i.v. doses does not differ in the dog, but in rats the former is lower than the latter. Plasma C_{max} and AUC increase almost proportionally with

the dose after a single dose in all species. After repeated administration AUC increases proportionally with the dose in the rabbit, higher than proportionally in the rat. By contrast in the dog the plasma AUC of atosiban decreased after daily doses of 2, 6 and 20 mg/kg.

Binding to plasma proteins is moderate, the highest value being reached in the dog (37-52%), which is close to that reported in man (46-48%). In rats it mainly locates in well-vascularised tissues, less in the placenta, and even less in the brain. The foetal-to-maternal AUC ratio averages 0.01-0.02 in rats and rabbits and about 0.12 in humans.

Atosiban undergoes sequential hydrolysis of C-terminal amino acids. This gives rise to several metabolites, which differ qualitatively and quantitatively between species. M1 metabolite (arising from the loss of glycine-ornithine from the molecule) is the most abundant and the only one that retains biological activity. M1 and M3 are present in human body fluids.

After i.v. injection in the rat atosiban is excreted predominantly in the faeces (54% vs. 24% in the urine at 24 hours); doses comparable to therapeutic ones are excreted almost completely within 72 hours. In the dog elimination in the urine equals that in the faeces.

Excretion of atosiban in the milk has not been investigated in animals.

Toxicology

The toxicity of atosiban was studied in mice, rats, guinea pigs, rabbits, and dogs. Bridging studies of acute and repeated toxicity demonstrated that the toxic potential of the compound used in these tests, prepared by solid phase peptide synthesis (SPPS), did not differ markedly from that of the product subsequently developed by a liquid phase peptide synthesis (LPPS).

Single dose toxicity

The maximum non-lethal dose in rats/mice (100 mg/kg i.v.) is about 20 to 40 times the therapeutic dose (5.5 mg/kg in women of 60 kg b.w. over 48-hour treatment and 2.5 mg/kg over 18 hour treatment). The intravenous dose of 10 mg/kg was well tolerated in female mice and rats. Single-dose toxicity studies demonstrated a moderate acute toxicity of atosiban with clinical signs related to the CNS, for example, in mice, tremors, decreased activity, ptosis and urine-stained coats were observed. In rats, sometimes, irritation, oedema, erythema, ulceration and necrosis were found at the injection site, probably due to atosiban diffusion into adjacent tissue and consequent vascular leakage.

In dogs the single intravenous dose of 10 mg/kg was well tolerated.

Repeat dose toxicity

Atosiban given daily to rats for two weeks did not induce systemic toxicity at doses up to 250 µg/kg (i.v. bolus) or 38.4 mg/kg (i.v. infusion ~10 times the daily dose in women). However, three out of 10 rats died in the highest dose group, while one animal died in the two lower dose groups and one in the control group.

Daily subcutaneous doses up to 20 mg/kg (for two week) in rats induced dose-related irritation at the injection site and primarily pharmacological effects. Irritation at the injection site was mainly swelling, ulceration and scab formation at all doses (> 2 mg/kg). The severity and incidence of irritation increased with the dose and the microscopic findings were fibroplasia associated with varying degrees of oedema, inflammation, and necrosis. The necrosis often led to loss of subcutaneous fat tissue (panniculus). After the recovery period fibroblast proliferation was still evident in the subcutaneous tissue. Mild to moderate decreases in total protein, albumin, urine volume, and increased urine osmolality and/or specific gravity were observed at 20 mg/kg. These observations are related to the antidiuretic activity of atosiban at these high dosages.

In rabbits at doses up to 250 µg/kg (i.v. bolus – for two weeks) only mild discoloration at the injection site was observed.

In dogs, i.v. infusion of atosiban at doses up to 0.04 mg/kg/mn, 16 h/day for 14 days (38.4 mg/kg/day, equivalent to 10 times the human dose) was well tolerated and did not cause deaths or reduce the animals' activity. Results in controls and atosiban-treated groups were similar, except for emesis. In dogs, s.c. administration of atosiban (up to 20 mg/kg/d for two weeks) provoked granulomatous inflammation at the injection site at all doses > 2 mg/kg; inflammation resolved completely in dogs

given 2 and 6 mg/kg/day and partially at 20 mg/kg. Increased activities of liver enzymes were observed at the highest dose after 6 and 13 weeks of treatment, without concomitant histological changes in the liver.

Furthermore, the Applicant presented two other studies in sheep: continuous infusion of atosiban to the foetus in utero in an acute (3 h, with doses up to about 6 μg/kg/min) and a repeated-dose study (14 days, with dose allowing to reach concentrations between 18.6 and 26.3 ng/ml). Sheep were chosen because the development of sheep kidneys resembles human foetal development more closely than the species commonly used in pregnancy toxicology.

In summary, no major unexpected toxicological findings were associated with repeated administration of atosiban in rats and dogs at dosages up to 20 mg/kg. Dose-related irritation was the major toxicological finding in both species. In rat, atosiban induced an antidiuretic effect high doses. The NOAEL was 6 mg/kg/day in the rat and 6 mg/kg/day in the dog 13-weeks subcutaneous studies.

Genotoxicity

A complete battery of *in vitro* and *in vivo* tests was run to assess the mutagenic potential of atosiban: bacterial gene mutation (*Salmonella typhimurium* and *E. coli)*, mammalian cell gene mutation at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary (CHO) cells, unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro*, chromosomal aberrations in CHO cells *in vitro* and *in vivo* micronucleus test in mouse with doses up to 150 mg/kg i.v.

Atosiban had no mutagenic effects on microbial or mammalian cells *in vitro* with or without metabolic activation.

In the bone marrow micronucleus *in vivo* test in mice, the drug did not increase the number of micronucleated polychromatic erythrocytes. The high dose of atosiban induced marked bone marrow toxicity, reducing the ratio of polychromatic-to-normochromatic erythrocytes, indicating sufficient exposure to the test compound.

In general, atosiban appears to lack any genotoxic potential.

Carcinogenicity:

Carcinogenic effects were ruled out in a two-year study in female rats exposed to daily s.c. doses up to 15 mg/kg. The highest tolerated dose of atosiban was based on the severity of the local irritation observed in three months' treatment with 20 mg/kg.

There were no treatment related deaths and body weight gain was not affected by atosiban. Irritation at the injection site was found in all groups including the vehicle controls, but necrosis, ulcers, thickening and oedema were observed at the highest dose. An increase of benign fibromas (incidence 6% *vs.* 0%) and malignant fibrosarcomas (29% *vs*. 0%) was found at the injection sites of the same group in comparison to the vehicle controls. Rodents, however, are particularly prone to local sarcomas induced by repeated injection of irritating materials.

The NOAEL in the two year study was 2.5 mg/kg, far above the maximum possible load in women in the very short course of administration (≤ 48 h).

Reproduction Toxicity

1. Fertility and general reproductive performance were not investigated considering the proposed utilisation of atosiban.

The evaluation of the teratogenic/embryotoxic potential of atosiban given subcutaneously to rats (25*,* 50 and 100 mg/kg on days 6 to 17 of gestation) and rabbits (10, 25 and 50 mg/kg on days 7 to 19 of gestation) showed a dose-related irritation at the site of injection in rats (at 50 and 100 mg/kg), but no drug-related effects on reproductive or foetal parameters; in rabbits, no maternal or embryo-foetal toxicity was found. In rats, the NOAEL was 25 mg/kg and 100 mg/kg for dams and foetuses respectively, and in rabbits and 50 mg/kg for both maternal and embryotoxic/teratogenic effects.

In the first subcutaneous study, very high dosages (100-, 200- and 300 mg/kg/day – from day 15 to 20 of gestation) were used, resulting in severe dosage-related dermal irritation in the dams and concomitant impairment of body weight gain. At 200- and 300 mg/kg/day, effects on viability and growth, and transient effects on development, were observed in the pups.

In intravenous studies, there were no significant findings up to doses as high 38.4 mg/kg/day (from day 15 to 20 of gestation). An increase in the incidence of dead pups in the infusion studies was attributed to complications associated with the infusion procedure.

In order to mimic the administration of atosiban in women towards the end of pregnancy, female rats were treated from day 15 to day 21. At high doses (200 and 300 mg/kg/day) the greater mortality of the pups might be due to irregular lactation (retention of milk in the first days after delivery) and/or maternal care. In these studies the NOAEL of atosiban was 100 mg/kg for adverse effects on dams and the litter.

The highest mean blood concentrations, C_{max} of atosiban were 8872, 13625 and 20001 ng/ml in dams and 75, 107 and 106 ng/ml in foetuses respectively for dosages of 100, 200 and 300 mg/kg/day, indicating a limited and saturable placental transfer of the drug.

Local Tolerance

Local tolerance studies were conducted in female rats, dogs and rabbits using either the subcutaneous or the intramuscular route.

Single s.c. doses of = 25 mg/ml or higher caused irritation in rats without signs of necrosis. Doses of 12.5, 25 and 50 mg/kg proportionally increased a subcutaneous irritation and degeneration of the panniculus in rats, and this was reversible by day 8 in the low-dose group.

Studies in dogs (s.c.) and rabbits (i.m) showed moderate to mild irritation.

Other toxicity (antigenicity, immunotoxicity and dependence) studies

An antigenicity study in guinea pigs and a passive cutaneous anaphylaxis test in rats did not elicit any positive response.

Discussion on toxico-pharmacological aspects

Atosiban is a high-affinity, competitive, though non-selective, antagonist of oxytocin (OT) receptors and arginine-vasopressin (AVP) receptors. All important functional systems have been investigated, and no atosiban-induced effects that could cause safety concerns for the proposed human use have been identified. The metabolite M1 appears to have a similar pharmacological potency as the parent compound.

However, the relative antagonistic potency of the liquid-phase peptide synthesis preparation (LPPS, intended for human use) and the solid-phase peptide synthesis preparation (SPPS, employed in pre-clinical in vitro tests) on human OT and AVP receptors is still not known. The two preparations have never been directly compared in experiments on human tissues; indirect comparisons suggest there is no real difference with regard to inhibition of the OT effect on human tissue, but direct comparisons on animal tissue suggest potential difference.

Absorption of atosiban after s.c. administration is fast (≤ 30 min) in all species tested (female rats, rabbits and dogs).

Atosiban undergoes sequential hydrolysis of C-terminal amino acids. This gives rise to several metabolites; among those the most abundant, M1 metabolite is the only one that retains pharmacological activity. M1 and M3 are present in human body fluids.

After i.v. injection in the rat atosiban is excreted predominantly in the faeces (54% vs. 24% in the urine at 24 hours); doses comparable to therapeutic ones are excreted almost completely within 72 hours. In the dog elimination in the urine equals that in the faeces.

Excretion of atosiban in the milk has not been investigated in animals.

Toxicity studies showed toxic effects only at doses with acceptable margins to the planned therapeutic dose range. There is no concern for target organ toxicity.

Reproduction toxicology studies did not identify cause for concerns for the proposed human use.

No genotoxic potential of atosiban was identified in a battery of tests. The carcinogenic potential (sarcomas at the injection site) identified in female rats at very high doses is not relevant for the human situation.

All local tolerance and antigenicity studies have proved that atosiban does not provoke strong reactions in animal and suggest atosiban is not likely to provoke topical adverse reactions during therapy.

4. Clinical aspects

Atosiban is an antagonist of oxytocin receptors.

The approved indication is:

"Atosiban is indicated for delay of imminent premature 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 24 until 33 completed weeks,
- a normal foetal heart rate."

Pharmacodynamic and pharmacokinetic data have been provided from both studies in healthy women and in women with preterm labour. The clinical documentation includes three small dose-selection studies. Documentation of efficacy is based on the CAP-001 studies, three randomised double-blind trials of atosiban *vs.* three different beta-mimetics, ritodrine, terbutaline and salbutamol. The single studies were designed so as to allow a final pooled comparative analysis of atosiban and beta-mimetics. In CAP-001, 361 patients received atosiban. Information on safety is available for 1260 atosiban treated women.

Clinical pharmacology

Primary pharmacodynamics were studied in healthy women and in women with premature labour. Pharmacokinetics of atosiban has been investigated in both normal healthy women and pregnant women.

Pharmacodynamics

Some of the clinical pharmacology studies were conducted in the mid 1980s prior to GCP regulation.

Primary effects in healthy women

Two studies from the late 1980s in menstruating healthy women used infusion of lysine vasopressin, which induces an increase in uterine activity and dysmenorrhoea-like symptoms. Atosiban and other oxytocin/vasopressin receptor antagonists were given as i.v. bolus (10μg/kg). As assessed by recording intrauterine pressure, atosiban was the most effective in terms of complete inhibition of contractions during the first 10 minutes after injection and had also the longest duration of inhibition (40-50 min). Vasopressin induced contractions are associated with a decrease in endometrial blood flow. Atosiban resulted both in an increase in uterine blood flow and relief of the dysmenorrhoea-like symptoms.

Another early study investigated atosiban's effect on primary dysmenorrhoea. The same dose as bolus was compared in a double-blind placebo controlled crossover study. Atosiban induced a short pain relief (30 min).

Primary effects in women with premature labour

Two pilot studies published 1987 and 1989 were conducted in patients with preterm labour (PTL) with atosiban at varying infusion rates and duration. None of the early clinical studies have established the optimal dosing schedule.

The first included 13 women with PTL (28-36 weeks GA) who were treated with atosiban at infusion rates of 10-100 μg/min for 1-10 hours. A marked decrease of uterine contractions on tochographic recording was observed in all patients with 6/13 having a total inhibition of contractions at an infusion rate of 25 to 100 μg/min over 2 to 10 hours. Atosiban had no adverse effects on maternal or foetal heart rate and maternal blood pressure was unaffected.

The second study included 12 women (27-36 weeks GA). Atosiban was given at infusion rates of 25-100 μg/min for 1.5-13 hours. Complete tocolysis was achieved in 6/12 patients at an infusion rate of

25 to 100 μg/min over 8 to 13 hours. At these infusion rates atosiban was quite safe with no maternal or foetal adverse effects.

Pharmacokinetics

Pharmacokinetics of atosiban has been investigated in both non-pregnant and pregnant women. Placental transfer of atosiban has also been studied. Plasma kinetics have been studied both with single i.v. bolus and different infusion schemes. Some of the studies also included kinetics after s.c. administration and one of the very early studies included intranasal administration.

Except earlier studies, plasma concentrations were assayed with radioimmunoassay using a specific antibody.

Absorption/distribution

The bioavailability of atosiban is poor after intranasal administration. In contrast, high (97±17 %) and linear to the dose absorption was demonstrated after s.c. administration, though with some inter-subject variability.

Following i.v. administration, steady state concentrations are rapidly reached (≤ 2 h) in non-pregnant women. 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.

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).

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

According to a study using a non-specific antiserum, after i.v. injection atosiban distributes according to a two-compartment model. The alfa-phase is fast (mean 8 min) and limited to body water with minor tissue binding.

Plasma protein binding of atosiban is 46 to 48 % in pregnant women. It is not known whether the free fractions in the maternal and foetal compartment differ substantially.

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 foetal/maternal atosiban concentration ratio was 0.12. The major metabolite M1 also crosses the placenta.

Small amounts of atosiban have been shown to pass from plasma into the milk of lactating women. Metabolite M1 is also excreted in milk. The plasma/milk ratio and the absolute concentrations in the milk of atosiban and its active metabolite M1 are not known.

Metabolism

Atosiban gives two main metabolites, M1 and M3, identified in plasma and urine samples of non-pregnant and pregnant women. M1 but not M3 is pharmacologically active in animals. The ratio of M1 to atosiban plasma concentrations ranged from 0.8-3.3 at different times and after different dosages. It is not known whether M1 accumulates in tissues. In foetal plasma samples the ratio of M1 to atosiban averaged 1.8. No absolute values are provided for maternal and foetal M1 plasma levels. M3 was detected in small amounts in plasma and urine of 23 pregnant women.

Elimination

The parent compound is found in only small quantities in urine, where its concentration is about 50 times lower than that of M1. The proportion of atosiban eliminated in faeces is not known.

Plasma clearance of atosiban is independent of the dose and ranged from 23 to 39 l/min in healthy volunteers and 42 to 47 l/min in pregnant women enrolled in different studies. Elimination half-life varied widely in studies in non-pregnant volunteers (from 15 to 80 min) and was longer in pregnant women (102±18 min).

In healthy subjects the elimination half-life ($t_{1/2\beta}$) of atosiban after different i.v. doses differed widely among studies: from 15±2.4 min to 79.7±15.6 min.

After 7.5, 15 and 30 mg s.c. the elimination half-life was two-fold longer than after 7.5 mg i.v. The elimination half-life was significantly longer during pregnancy: 102±18 min.

There are no data from special populations (renal or hepatic impairments). This lack of experience has been stated in the SPC.

Interaction studies:

Two *in vitro* studies have assessed the effects on selected cytochrome P450 isoenzymes in human liver microsomes. The results indicated that atosiban is unlikely to cause significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 activities in vivo.

The possible interaction between atosiban and antibiotics, antihypertensives (including diuretics), ergot alkaloids, or steroids was investigated by logistic regression analysis using the data from the three CAP-001 studies. The apparent lack of interaction cannot be considered definitive because of the scant data. This lack of data is stated in the SPC and the Marketing Authorisation Holder will further investigate the possible interactions between atosiban and antibiotics, antihypertensive agents, ergot alkaloids and steroids.

Clinical efficacy

Three dose-selection studies are included.

The efficacy claim is based on the results of three pivotal double-blind controlled trials, and particularly on their pooled analysis (Protocol CAP-001), comprising 733 patients. The results of two other studies, a placebo controlled one (PTL 096) and an open label one (PTL-098), are also presented. These studies are presented in the table below:

Study	No patient /treatments	Type of trial
CAP 001/atosiban vs ritodrine	Atb: 126 Rti: 121	double blind, double dummy randomised trial
CAP 001/atosiban vs terbutaline	Atb: 119 Terb: 122	double blind, double dummy randomised trial
CAP 001/atosiban vs salbutamol	Atb: 107 Salb: 107	double blind, double dummy, randomised trial
PTL 096 atosiban vs placebo	Atb: 250 Pbo: 251	Double blind, double dummy, placebo-controlled randomised trial
PTL 098 atosiban in acute phase	Atb: 649	Open-label acute treatment. Successfully treated patients continued in a randomised double-blind parallel-group, placebo controlled phase.

All studies of CAP-001 were conducted in accordance with the GCP requirements.

Dose-response studies and main clinical studies

Dose response studies

A randomised, double-blind study compared placebo and atosiban 300 µg infusion for two hours in patients with PTL, 59 patients in each treatment arm. 5 different protocols were used. A reduction of 40% or greater in number of uterine contractions was seen in 43 of 56 atosiban treated (76.8%) compared to 18 of 56 placebo treated (32,1%) The number of contractions decreased 55.3±36.3% and 26.7±40,4% respectively in the two groups. Atosiban was only statistically significantly superior to placebo in GA > 31 weeks, whereas placebo was better, although not statistically significant, in a small group with a GA< 28 weeks (n=14). Four patients in the atosiban group developed either vomiting, diarrhoea or nausea compared to 1 in the placebo group.

Open study of Atosiban infusion 300 µg/min in 62 patients with PTL. Due to the lack of control group and variations in the inclusion criteria, the study contains little information.

The recommended posology has been mainly selected on a dose finding study (L91/049) conducted after the two above-mentioned phase II studies.

In the L91-049 study, the patients were randomly allocated to one of the four atosiban schedules groups or to one open-label ritodrine group as follows:

- atosiban 6.5 mg bolus + 300 µg/m infusion;
- placebo bolus + atosiban 300 µg/min infusion;
- atosiban 2 mg bolus + 100 µg/min infusion;
- atosiban 0.6 mg bolus + 30 µg/min infusion;
- ritodrine.

Atosiban infusion was continued for up to 12h, if useful.

The bolus was given in order to achieve target plasma concentrations of atosiban sooner than with infusion alone. The results of L91-049 study are shown in the table below.

Summary of efficacy results in study L91-049

	6.5 mg + 300 µg/min (N=63)	Placebo + 300 µg /min (N=59)	2 mg + 100 µg /min (N=64)	0.6 mg + 30 µg /min (N=58)	Ritodrine (N=58)
Proportion of subjects whose contractions stopped during treatment	36/63 (57.1%)	35/58 (60.3%)	42/64 (65.6%)	29/58 (50.0%)	41/58 (70.7%)
Time to stopping of contractions (Wilcoxon rank sum test) in hours	3.0±2.4	4.9±3.2	4.4±3.4	4.8±3.0	2.6±2.0
Proportion of subjects with contractions of ≤4/h at end of treatment	43/61 (70.5%)	41/58 (70.7%)	44/63 (69.8%)	32/56 (57.1%)	44/56 (78.6%)
Proportion of subjects with labour arrested for two days	42/63 (66.7%)	34/59 (57.6%)	41/64 (64.1%)	34/58 (58.6%)	34/58 (58.6%)

The above data suggest that 6.5 mg + 300 µg/min take less time to stop contraction than placebo + 300 µg/min, 2 mg + 100 µg/min or 0.6 mg + 30 µg/min, but the findings regarding the proportions of women whose contractions stopped during treatment, with contractions =4/h at the end of treatment or with labour arrested for two days, do no show any clear pattern. Due to the small sample the large CI of these proportions do not allow any firm conclusion. Furthermore, the importance of reducing time to stopping contraction as a clinical outcome is questionable. For example, in this trial ritodrine was superior to 6.5 µg + 300 µg/min of atosiban in stopping contraction early.

On this basis, the company chose to investigate the following dose regimen: Single bolus injection of 6,75 mg followed by a rapid infusion of 300 µg/min for 3 hours, after that the infusion rate was decreased to 100 µg/min for up to 48 hours.

Main study: Protocol CAP-001

CAP-001 consists of three phase III, multicentre, multinational, double blind, double dummy, randomised parallel group, controlled trials. The three CAP-001 studies have a similar general design. However the comparison groups differ, using three beta mimetic drugs: ritodrine, terbutaline and salbutamol. The three studies were conducted between 1992 and 1997. A pooled analysis of the three studies was planned before they were started. Randomisation was stratified according to GA > 28 weeks and ≤ 28 weeks.

The three CAP-001 studies enrolled women with:

- PTL diagnosed by the presence of regular uterine contractions of at least 30 seconds duration at a rate of =4 per 30 minutes confirmed by external tocography, cervical dilatation of 1-3 cm and effacement of =50% (0-3 cm cervical dilatation for nulliparae);
- age =18 years or age of legal consent;
- GA between 23-33 completed weeks;
- ultrasound-confirmed normal presentation of one or two normal foetuses.

Seven hundred and forty-two patients were enrolled and 733 received study drug treatment (361 with Atosiban and 372 with beta-mimetics). Atosiban was administered in the dose regimen intended for marketing authorisation: *Single bolus injection of 6,75 mg followed by a rapid infusion of 300 μg/min for 3 hours, after that the infusion rate was decreased to 100 μg/min for up to 48 hours*. The duration of infusion was up to 18 hours in the Ritodrine and Terbutaline studies and up to 48 hours in the Salbutamol study.

For ethical reasons patients could be treated with rescue treatment with an alternative tocolytic if required.

Retreatments were allowed with the same study medication provided that no alternative treatment was given and the GA was below 34 weeks. Patients who discontinued due to adverse events were still eligible for re-treatment unless they fulfilled the criteria for initial treatment failure.

The primary parameter of efficacy considered was the time to failure (TTF), defined as the time from the start of study therapy to treatment failure, defined as the earlier of either:

- the time point for the first alternative tocolytic therapy;
- or delivery.

The analysis focussed on the proportion of women with TTF>7 days.

The sample size of the CAP-001 studies was based on the proportion of patients delivering within 7 days from treatment.

Secondary efficacy endpoints included:

- TTF > 48 hours,
- Gestational Age at delivery,
- Initial treatment failure/success during the first cycle defined as the proportion of patients who were initial treatment successes after completion of drug administration (defined as a reduction in the progression of labour).

Other variables were: Time to delivery TTD, Time to alternative tocolytic (TTAT), Number of days to first recurrence, only for patients with initial treatment success in the first cycle.

Other secondary objectives were to compare: Infant birth weight, Number of days in neonatal intensive care and number of days spent on a ventilator, Total number of days spent in a nursery, Frequency of hyaline membrane disease, Frequency of major illness/handicaps, Number of deaths.

Results of the individual trials according selected endpoints (ITT analysis):

Protocol CAP-001\C and I	Atosiban	**Ritodrine***	P
Number of patients in the ITT population	118	114	
Early terminations	23.9%	40.5%	
48 hour treatment success (TTF > 48h)	86 (72.9%)	75 (65.8%)	0.241
TTF > 7 days	77 (65.2%)	61 (53.5%)	0.017
TTF, Gain in GA (days), median	37.9	11.9	0.049
Median time to delivery, (days)	34.0	37.2	

* *Ritodrine was initially infused at a rate of 0,1 mg/min, the dose gradually increased until contractions stopped or the maximal dose of 0,35 mg/min was reached. The infusion was continued at the maximally effective dose for a period of 12 hours. The duration of drug treatment was up to 18 hours, mean 14 hours.*

Protocol CAP-001\UK and S	Atosiban	**Terbutaline***	P
Number of patients in the ITT population	113	121	
Early terminations	22.4 %	18.6 %	
48 hours success (TTF > 48 h)	72.3 %	68.6 %	0.534
TTF > 7 days	62 (55.4%)	52 (43.0%)	0.094
TTF, Gain in GA (days), median	14.4	4.3	0.293
Median time to delivery (days)	43.0	35.5	

** Terbutalin was given at an initial rate of 5-10 µg/min, with increments every 10-20 minutes to a maximum of 20-25 µg/min. The maximal effective dose was continued for 12 hours, the total infusion time was not to exceed 18 hours.*

Protocol CAP-001\A and F	Atosiban	**Salbutamol***	P
Number of patients in the ITT population	107	108	
Early terminations	16.8 %	13.9 %	
48 hours treatment success (TTF > 48 h)	78.5%	74.8%	0.518
TTF > 7 days	62 (57.9%)	50 (46.7%)	0.041
TTF, Gain in GA (days), median	13.5	5.3	0.0590
Median time to delivery (days)	45.3	45.5	

** Salbutamol infusion was started with an initial rate of 2,5-5 µg/min and increased gradually to a maximum of 25 or 45 µg/min. The maximal infusion rate was continued for 24 hours, the total infusion time maximally 48 hours corresponding to the study duration.*

Discontinuations due to insufficient efficacy (CAP-001 studies)

Study	Atosiban	Beta-mimetics
CAP-001\Ritodrine	18 %	10 %
CAP-001\Terbutaline	9 %	5 %
CAP-001\Salbutamol	13 %	6 %
Pooled analysis	14 %	6 %

Results of the pooled analysis

Overall the efficacy analysis of CAP-001 studies enrolled 681 patients, similarly distributed in the three studies.

The proportion of discontinuations due to insufficient efficacy was 14 % in the Atosiban group compared to 6 % in the Beta-mimetics group (as described in the previous table).

The pooled analysis of CAP-001 studies showed that the proportion of women with TTF > 7 days was higher in the atosiban than the beta-mimetics group (201/337 [59.6%] with atosiban, 163/342 [47.7%] with beta-mimetics, OR 1.62. 95% CI 1.18-2.23, p=0.002).

The median number of days from initiation of therapy to treatment failure was longer in the Atosiban group (19.3 days) than in the Beta-mimetics group (5.53 days), (p=0.0082). The TTF>48 hours was higher in the Atosiban group (74.5% versus 69.3%, p=0,038).

No improvement was observed in the pooled analysis in mean gestation age at delivery or in foetal or infant main outcome parameters (birth weight, survival, frequency of respiratory distress syndrome (RDS), intracranial haemorrhage).

	Atosiban	**ßeta-mimetic**
Mean gestational age at delivery (days)*	249	247
Mean birth weight (g)**	2490	2461
Infant deaths (%)**	1.2	2.3

Frequency of RDS (%)**	19	20
Intracranic haemorrhage (%)**	4	5

* *based on efficacy population: Atosiban; 337 women, ß-mimetic; 341.*
** *based on safety population: Atosiban; 406 infants, ß-mimetic; 432*

Results in early gestational age

The CAP-001 studies showed that the probability of TTF >7 days was not statistically significantly higher among women at gestational age <28 weeks (51,6% in atosiban group compared to 32.8 % in beta-mimetics group, OR 2.43, 95% CI 0.91-6.47, p=0.076), while it was so in later stages of pregnancy (OR 1.62, 95% CI 1.13-2.24, p=0.009). Notably the three CAP-001 studies included only 129 patients at gestational age <28 weeks who were randomly assigned to atosiban or the three comparators. Furthermore, there was no difference in TTF in women with gestational age 23 - 27 weeks treated with atosiban or placebo in the PLT-096 study.

Twins

Clinical experience in twin pregnancies was limited, therefore it should be stated in the product information that the use of atosiban in this situation is uncertain and should be used with caution.

Other studies

Study PTL-096 was a placebo-controlled study in 531 participants with Gestational Age 20-33. The primary parameter of efficacy considered was also the time to failure (TTF). The study was characterised by imbalance at randomisation (differences in GA at inclusion and in severity of PTL) and approximately 20% had received alternative tocolytic treatment before evaluation of treatment success/failure was performed. Due to these methodological issues, the results should be taken in consideration with caution. The proportion with treatment success after 24 hours, 48 hours, and 7 days favoured Atosiban over placebo. Compared to placebo, the time to delivery or therapeutic failure was not increased.

The PTL 098 study was an open-label study of Atosiban in the proposed dose but followed by s.c. administration. It was not randomised trial in the acute phase; randomisation with placebo being done only for the maintenance phase. Therefore, in this study there are no comparative data that can be used for efficacy information relevant to acute treatment of pre-term labour.

Discussion on clinical efficacy

The recommended dosage and schedule of administration was chosen on empirical basis. No systematic and accurate disposition profile of atosiban was described, particularly during pregnancy. No relationship was clearly established between plasma concentrations and effects. The amount of drug needed to reduce uterine activity was empirically chosen with no kinetic-dynamic basis. The different dosages and schedules tested did not differ with respect to clinically relevant outcome measures such as the proportion of women whose contractions stopped during treatment or who had ≤ 4 contractions by the end of treatment or whose labour was arrested for two days. The alleged reduction of time to stopping contractions by the recommended dosage does not apparently mean an advantage compared to ritodrine. The suggested infusion of 100 mg/min after the first 3-h treatment has no apparent experimental basis. The proposed regimen has not been proved to be better than lower-dose regimens or as effective as and less toxic than higher-dose ones.

Using the TTF as main efficacy criteria is questionable since it compounds the efficacy/safety profile of study drugs. The longer TTF reflects the better tolerability of atosiban compared to beta-mimetics. TTF is longer because patients on atosiban need to shift to alternative tocolytics less often than those using beta-mimetics. However, discontinuation of the assigned treatment due to insufficient efficacy was more frequent in the atosiban group (48/338 vs. 20/343, OR 2.67, 95% CI 1.50-4.78, p=0.0003). In addition, the proportion of patients with an initial success rate was lower in the atosiban group (82% vs 88%, -6%, 95% CI -11 to -1, p=0.025). This suggests that atosiban may be less effective,

even though better tolerated. One has to assume that the better tolerability is not the result of an investigators' bias – randomised treatments were easily identifiable because of the cardiovascular side effects of beta-mimetics.

In the three CAP-001 studies, only 129 patients at gestational age < 28 weeks were randomly assigned to atosiban or beta-mimetics. The proportion of women in this subgroup with TTF > 7 was not statistically significantly higher in the atosiban group. The use of atosiban in early pregnancy is based on little clinical experience.

Clinical safety

Both safety data in treated women and infants have been assessed.

Patient exposure

Main information on safety derives from:

Group 1) the comparative studies (CAP-001 protocol) *vs* beta-mimetics for a total of 361 patients given atosiban and 372 given beta-mimetics;

Group 2) patients treated with atosiban (total of 899) included in the PTL-096 placebo controlled study and in the open label study PTL-098.

Overall, information on safety is available for 1260 atosiban treated women. The main evidence, however, as for efficacy, comes from the pooled analysis of the CAP-001 protocol.

Adverse events (AE) and serious adverse event/deaths

Maternal adverse events

With regard to serious maternal AE during atosiban i.v. treatment, only one case (an allergic reaction) was defined as related to atosiban.

Although chest pain, myocardial ischemia, dyspnea, tachycardia (etc.) were less frequent in the atosiban group, pulmonary oedema, the most dangerous of the beta-mimetic-related AE, was reported in two patients in the overall safety population given atosiban as well as in the beta-mimetic groups in CAP-001 studies. These events were presumably caused when patients assigned to atosiban shifted to beta-mimetics. It is noteworthy that despite the high rate (at least one third) of shifts to beta-mimetics in the CAP-001 studies, only 11 patients in the overall safety population (n=1260) discontinued atosiban due to maternal AE.

In the overall safety population, there was no increased risk of atoni, uterine haemorrhage or vaginal haemorrhage at the delivery.

The most frequently reported maternal AEs (Group 1 and 2) were:

Frequency (%)	Atosiban (n=1260)	Beta-mimetics (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
Urinary tract infection	2,3	4,8	0,4

The general findings of the pooled analysis and PTL 096 and 098 studies suggest that the frequency of maternal mild adverse events is lower with atosiban than in the beta-mimetics group and slightly higher than in the placebo one.

Fetal AE

Most frequently reported foetal AEs (atosiban and beta-mimetics, Group 1 and 2)

Frequency (%)	Atosiban (n=1260)	Beta-mimetics (n=372)	Placebo (n=251)
Bradycardia	2.6	3.5	1.6
Foetal distress	1.1	3.8	0
Tachycardia	0.9	26.3	0
Asphyxia	0.1	0.8	0

The only AE with a lower incidence in the overall safety population and in the subgroups of CAP-001 without alternative tocolytic treatment was tachycardia. There were 29 serious foetal AE (6 deaths) in atosiban groups from the phase III studies. In the active control CAP-001 studies neither serious AE (n=18) nor deaths (n=1) in the atosiban group differed from those in the beta-mimetic groups (22 and 2, respectively). Five discontinuations due to foetal AE (foetal distress and "deceleration") were reported in the PTL studies.

Infant AE

In the infant population, there was as expected in this population with premature birth a high number of AE.

Infant mortality did not differ in atosiban and control patients (19/985 vs. 19/999) in the overall safety population or between the atosiban and beta-mimetic groups in the CAP series (5/406 vs. 10/432, p=0.24).

Congenital abnormalities (8.9% in atosiban and 8.8% in control groups) and serious AE (8.8% vs. 8.2%) were also distributed equally.

Considering the CAP-001 protocol (group 1), the frequencies of neonatal death, RDS, apnoea, hypoglycaemia, neonatal sepsis, and cerebral haemorrhage were similar in the atosiban and beta-mimetic groups.

Most frequently reported infant AE (Group 1 only)

Frequency (%)	Atosiban (n=406)	Beta-mimetics (n=432)
Resp. distress syndrome.	19	20
Apnoea	9	5
Anaemia neonatal	8	8
Hypoglycaemia neonatal	6	6
Sepsis neonatal	6	8
Cerebral haemorrhage	4	5

Considering the information from group 1 and 2, higher frequencies of RDS and respiratory disorders were reported in the atosiban than beta-mimetics groups.

Most frequently reported infant AEs[1](Group 1 and 2)

Frequency (%)	Atosiban (n=1404)	Beta-mimetics (n=430)	Placebo (n=292)
Resp. distress syndrome	21	17	23
Resp. Disorder	14	2	22
Bacterial infection	11	1	12
Apnoea	11	4	9
Anaemia neonatal	9	7	8
Sepsis neonatal	2	6	<1
Hypoglycaemia neonatal	8	5	8
Bone disorder	5	<1	9

[1] *stillbirths are not included in this analysis*

Respiratory distress syndrome was the most frequent AE. Its incidence did not apparently differ between treatment groups in the overall safety population, with the possible exception of the PTL-096 study. In this study a non significant excess of risk was reported for atosiban compared to placebo (64/288, 22% *vs.* 54/295, 18%). Nevertheless, a multivariate analysis of the possible confounding variables shows that the excess of infant deaths in the atosiban group in study PTL-096 was due to an imbalance in gestational age at delivery, not to the experimental drug or other factors.

Laboratory findings

In infants, no clinical adverse changes in laboratory parameters were seen.

Discussion on clinical safety

Data on the incidence of the main outcome measures and serious unexpected adverse events (birth weight, APGAR score, RDS, cerebral haemorrhage in infants, blood loss, uterine atony, placenta disorder and operative delivery in women, percentage of gestational age at delivery > 34 weeks) associated with atosiban treatment compared to other tocolytics are reassuring. There is no apparent excess of foetal, infant and maternal events in the atosiban group.

Nevertheless, it has been raised whether the pivotal studies designed to detect a difference in terms of time-to-failure (TTF) of the tocolytic treatments had enough power to rule out an excess of rarer, though clinically important, events. The table below shows the detectable differences in the incidence of such events.

OUTCOME MEASURE	ATOSIBAN	CONTROL	DETECTABLE ABSOLUTE DIFFERENCE*
Gestational age at delivery > 34 weeks	31 %	33 %	About 10 %
Caesarean section	14 %	19 %	About 8 %
Infant RDS	20 %	20 %	About 8 %
I Birth weight (mean g ± SD)	2491 ± 813	2461 ± 831	About 170 g

**α 0.05, β 0.20, sample about 800 patients*

5. Overall conclusion and benefit risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

The primary pharmacodynamic studies provided adequate evidence that atosiban is an antagonist of oxytocin receptors and may have an effect in pre-term labour. The general pharmacology studies showed no atosiban-induced effects that could cause concerns for the proposed human use. Overall, the toxicology programme revealed an acceptable safety profile without organ toxicity.

Efficacy

The apparent lack of interaction between Tractocile and antibiotics, antihypertensive agents, ergot alkaloids and steroids is based on limited data and will be further investigated, as outlined in the approved FUM.

The lack of effective drugs to retard preterm labour is a major obstetrical problem. Maternal and foetal side effects often limit treatment with beta-mimetics. Compared with these, atosiban offers no advantages in prolonging gestation, stopping contractions or improving foetal or maternal outcome. Atosiban has the same effect on surrogate parameters (contraction rate, time to stop contractions etc) as the reference treatment, but a better outcome for the foetus or mother has not been established.

However, discontinuation of the assigned treatment due to insufficient efficacy was more frequent and the proportion of patients with an initial success rate was lower in the atosiban group. This suggests that atosiban may be less effective, even though better tolerated.

Traditional dose-ranging studies have not been done, and the bolus dose, the loading dose and the maintenance dose could all be questioned, however the efficacy of the proposed dose regimen was shown in the phase III study. In the three CAP-001 studies, only 129 patients at gestational age < 28 weeks were randomly assigned to atosiban or beta-mimetics. The proportion of women in this subgroup with TTF > 7 days was not significantly higher in the atosiban group.

Safety

Atosiban has good maternal/foetal tolerability with little evidence of the adverse event (AE) commonly associated with tocolytic (beta-mimetic) agents. Although this is apparently reassuring for mothers and infants, it must be borne in mind that the comparative studies of phase III were small with respect to the aim of assessing differences in rare but important outcome events such as infant death or RDS.

Benefit/risk assessment

During an oral explanation held before the CPMP on 21 September 1999, the applicant addressed the following issues: the recommended dosage and schedule of administration, the acceptability of a possibly worse clinical outcome in the atosiban group compared to the beta-mimetic group and efficacy in early pregnancy.

Taking into account the following points:

1. the recommended dosage and schedule of administration although based on empirical conclusions from different studies, was tested and proved effective in phase III pivotal studies
2. in the pivotal studies the proportion of women remaining undelivered and not requiring alternative tocolytics within seven days of treatment initiation was higher in the atosiban than in the beta-mimetic group
3. the better outcome was due to better tolerability, although initial success rate was lower and discontinuations due to insufficient efficacy were more frequent in the atosiban group
4. atosiban has the same effect as beta-mimetics on surrogate endpoints (contraction rate, time to stop of contraction etc)
5. atosiban offers no advantage in prolonging the gestational age, stopping contractions and improving foetal and maternal outcome compared to beta-mimetics
6. subgroup analyses from clinical studies suggest that atosiban may be less effective in early gestational stages (≤28 weeks)

The CPMP has considered that atosiban is a suitable treatment in the prevention of pre-term labour.

Based on the CPMP review of available data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Tractocile in the treatment of delaying imminent pre-term labour 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 24 until 33 completed weeks
- a normal foetal heart rate.
- was favourable.