30 May 2013
EMA/476499/2013
Committee for Medicinal Products for Human Use (CHMP)

Atosiban SUN

Atosiban

Procedure No. EMEA/H/C/002329

Assessment report for initial marketing authorisation application

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 29 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Atosiban SUN, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data.

Information on paediatric requirements

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Tractocile 6.75mg/0.9 ml solution for injection.
- Marketing authorisation holder: Ferring Pharmaceuticals A/S
- Date of authorisation: 20/01/2000
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/99/124/001

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Tractocile 6.75 mg/0.9 ml solution for injection and 37.5 mg/5ml concentrate for solution for infusion
- Marketing authorisation holder: Ferring Pharmaceuticals A/S
- Date of authorisation: 20/01/2000
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/99/124/001-002

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturer

Manufacturer responsible for batch release

Sun Pharmaceutical Industries Europe B.V.

Polaris avenue 87

2132JH Hoofddorp

NETHERLANDS

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 29 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012.
- During the meeting on 14-17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of

Questions to all CHMP members on 24 April 2013.

- The summary report of the GMP/GCP inspection carried out at the following site Sun Pharmaceutical Industries Ltd., Baroda Highway, Halol-389350, Gujarat, India between 1-5 October 2012 was issued on 21 May 2013.
- During the meeting on 27-30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Atosiban SUN on 30 May 2013.

2. Scientific discussion

2.1. Introduction

Atosiban SUN, 6.75 mg/0.9 ml solution for injection and 37.5 mg /5 ml concentrate for solution for infusion is a generic medicinal product of Tractocile, which has been authorised in the EU since 20 January 2000.

The active substance of Atosiban SUN is atosiban, a synthetic peptide ([Mpa1, D-Tyr(Et)2, Thr4,Orn8]-oxytocin) which is a competitive antagonist of human oxytocin at receptor level. 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.

The safety and efficacy profile of atosiban has been demonstrated in several clinical trials. In addition, there is extensive post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Tractocile, no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Atosiban SUN is administered as an aqueous intravenous solution containing the same active substance as the currently approved product; therefore, a bioequivalence study versus the reference product Tractocile was not required according to the applicable guideline.

The indication proposed for Atosiban SUN is the same as authorized for the reference medicinal product: 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

The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

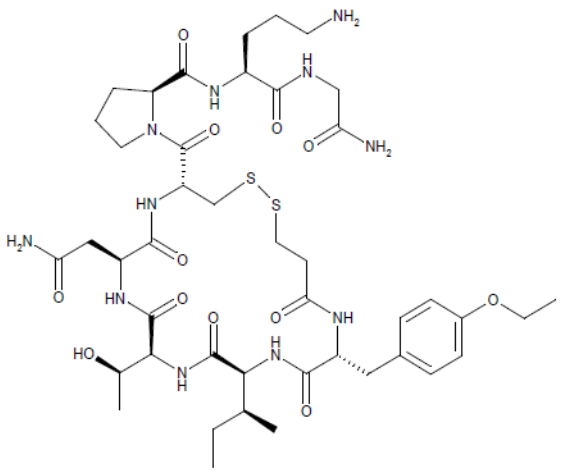
The finished product is presented as solution for injection and concentrate for solution for infusion containing 6.75 mg/0.9 ml and 37.5 mg/5ml, respectively of atosiban (as acetate) as active substance.

Other ingredients are: mannitol, hydrochloric acid and water for injections for both pharmaceutical forms.

The product is available in glass vial (type I) with bromobutyl flange rubber stopper and sealed with flip top aluminium seal.

2.2.2. Active substance

The chemical name of atosiban acetate is L-Glycinamide; cyclic(1—6)-disulfide, 3-mercaptopropionamide-D-tyrosyl(ethyl)-L-isoleucyl-L-threonyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-ornithyl (available as acetate salt) and has the following structure:



Atosiban acetate is a white or off-white powder, hygroscopic and soluble in water. Atosiban is a multi-chiral deca-peptide. The chiral centres are denoted in the structure of Atosiban. The chiral attribute of Atosiban is assessed by a specific optical rotation test. The specific optical rotation value ranges between -55° and -45°. Polymorphism has not been observed for atosiban.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Atosiban acetate is synthesised by one manufacturing site.

The Solid phase peptide synthesis of atosiban involves coupling of the amino acid components in sequential manner.The first amino acid is selectively bound to a polymer resin. The amino group is then selectively de-blocked and condensed with the next amino acid. This completed one cycle is then repeated sequentially for coupling of remaining 8 protected amino acids. The protected atosiban is cleaved and de-protected to obtain crude active substance. This crude product is finally purified and

the pure product obtained from HPLC purification is desalted and freeze dried to yield pure atosiban acetate.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for description, solubility, identification (molecular weight, UPLC), water content, related substances (UPLC), amino acids, assay (UPLC), peptide content, residual solvents, specific optical rotation, content of acetic acid (GC), clarity, colour index, content of trifluoroacetic acid (IC), bacterial endotoxins, bioburden test, total aerobic microbial count, total combined moulds and yeasts count. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Batch analysis data of three production batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 production batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up 24 (1 batch) and 18 (2 batches) months under long term conditions at -20 ± 5°C and for up to 6 months under accelerated conditions at 5°C ± 3°C according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, clarity, colour index, water content , specific optical rotation, content of dimethylformamide and dimethylacetamide, related substances, content of acetic acid, and assay. The analytical methods used were the same as for release and were stability indicating.The stability results indicate that the drug substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain a finished product comparable to the reference medicinal product Tractocile 7.5mg/ml concentrate for solution for infusion and Tractocile 7.5mg/ml solution for injection. The composition of Atosiban SUN concentrate and solution for injection is identical to the reference product with respect to both the active substance and the excipients. The relevant attributes (physicochemical characteristics and compatibility of the active substance with the excipients) of the drug substance that can influence the performance of the drug product were taken into consideration during development.

The manufacturing process comprises of bulk manufacturing in a vessel, aseptic filtration and filling. The choice of sterilisation method together with other critical process parameters was justified. The concentrate for solution for infusion was tested for compatibility with the following solutions as stated in the SmPC: 0.9%w/v NaCl, Ringer's lactate solution, and 5%w/v glucose solution.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging proposed is Atosiban Sun is packed in tubular glass vial (type I) with bromobutyl rubber stopper and sealed with flip top aluminium seal. Compatibility with the primary packaging material chosen is shown and a photo stability study has been presented. An extractables study was also performed on the rubber stoppers and there are no concerns. Container closure integrity has been shown by means of sterility testing and a microbial challenge test.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process comprises of bulk manufacturing in a vessel, aseptic filtration and filling.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for both pharmaceutical forms.

Product specification

The finished product release specifications for both pharmaceurical forms include appropriate tests for description, identification (UPLC, UV), identification for mannitol, pH, bacterial endotoxins (Ph Eur), particulate contamination, sterility (Ph Eur), extractable volume (Ph Eur), volume variation, % transmittance at 650 nm, absorbance at 420 nm, related substance (UPLC), assay of atosiban (UPLC), assay of mannitol (HPLC), cytotoxicity – in vitro biological reactivity test, and uniformity of dosage (Ph Eur).

Batch analysis results in six batches (three for each pharmaceutical form) of commercial scale confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of 3 production batches per pharmaceutical form of finished product stored under long term conditions for 12 months at 2ºC - 8ºC (upright and inverted) and for up to 6 months under accelerated conditions at 25 ºC ± 2ºC / 60% ± 5% RH according to the ICH guidelines were provided. The batches of Atosiban SUN are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Samples were tested for the following tests: description, pH, absorbance at 420 nm, % transmittance at 650 nm, related substance and assay of atosiban.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Atosiban SUN manufactured by SUN Pharmaceutical Industries Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all atosiban containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

In accordance with Article 10(1) of European Directive 2001/83/EC appropriate data is provided to support the claim that the proposed product is essentially similar to the originator with respect to both the solution for injection and the concentrate for solution of infusion. The qualitative composition is identical with that of the originator and the applicant's proposed SmPC is compliant with the reference product with no novel claims or dose recommendations. The impurity profile has been discussed and was considered acceptable. An adequate non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to the approval of Atosiban SUN 6.75 mg/0.9 ml solution for injection and 37.5 mg/5 ml concentrate for solution for infusion from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a solution for injection / concentrate for solution for infusion containing atosiban. . The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of atosiban based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

Exemption

The composition of Atosiban SUN is identical to the one of the reference product. It is an aqueous intravenous solution containing the same active substance in the same concentration as the reference product Tractocile. The excipients do not interact with the drug substance and do not affect the disposition of the drug substance otherwise. Therefore, in accordance with the guideline “Note or Guidance on the Investigation of Bioequivalence” (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1), there is no requirement for a bioequivalence study for such products.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented and no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data for Atosiban Sun are available. The medicinal product has not been marketed in any country.

2.4.5. Conclusions on clinical aspects

This is a generic medicinal product administered as an aqueous intravenous solution containing the same active substance as the reference product. The qualitative composition is identical with that of the originator and the applicant’s proposed SmPC is compliant with the reference product with no novel claims or dose recommendations. A clinical overview has been provided, which is based on up-to-date and adequate scientific literature. Therefore, the CHMP agreed that no bioequivalence studies or any other clinical studies are required.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1, the PRAC considers by consensus that the risk management system for Atosiban Acetate (Atosiban SUN) 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

is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

important identified risk	Nil
important potential risk	1. Fetal harm 2. Urinary Tract Infection (UTI) 3. Pulmonary Oedema
important missing information	1. Interaction with anti-hypertensive agents (except labetalol) and antibiotics 2. PKPD and safety profile in patients with impaired hepatic and renal functions 3. Safety in women less than 18 years of age

Pharmacovigilance plans

Safety concern	***Planned pharmacovigilance activities (routine and additional)***
Important Potential Risk	
Fetal harm	Routine pharmacovigilance with close review / monitoring of fetal events such as bradycardia, fetal distress, tachycardia, deceleration and asphyxia (including death).
Urinary Tract Infection	Routine pharmacovigilance with close review / monitoring of event of maternal Urinary Tract Infection.
Pulmonary oedema	Routine pharmacovigilance with close review / monitoring of event of pulmonary oedema.
Important missing information	
Interaction with anti-hypertensive agents (except labetalol) and antibiotics	Routine pharmacovigilance with cumulative review of any such interactions.
PKPD and safety profile in patients with impaired hepatic and renal functions	Routine pharmacovigilance with review of adverse events occurring in patients with impaired hepatic and renal functions.
Safety in women younger than 18 years old	Routine pharmacovigilance with review of adverse events in case of use in women below 18 years of age.

Risk minimisation measures

Safety concern	***Proposed risk minimization activities***
Important Potential Risk	
Fetal harm	Description under SPC sections 4.4:special warnings and precautions, 4.6 (subsection fertility) and section 5.1.
Urinary Tract Infection	None
Pulmonary oedema	Described under section 4.8 Undesirable effects

	(subsection post-marketing experience) and section 4.4 of SPC.
Important missing information	
Interaction with anti-hypertensive agents (except labetalol) and antibiotics	None
PKPD and safety profile in patients with impaired hepatic and renal functions	Described under section 4.2, 4.4, and 5.2 that "there is no or very limited experience with atosiban treatment in patients with impaired function of the liver or kidneys".
Safety in women younger than 18 years old	SPC section 4.2 (subsection: paediatric population) states "the safety and efficacy of atosiban in pregnant women aged less than 18 years have not been established. No data are available".

The CHMP endorsed this advice without changes.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of atosiban solution for injection and concentrate for solution for infusion, respectively. The reference product Tractocile is indicated to delay imminent pre-term birth in pregnant adult women. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The product is administered as an aqueous intravenous solution containing the same active substance as the reference product. The qualitative composition is identical with that of the originator and the

applicant's proposed SmPC is compliant with the reference product with no novel claims or dose recommendations. Therefore, no bioequivalence study is required.

Furthermore the proposed SmPC is consistent with the reference product with no novel claims or dose recommendations.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance 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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic safety update reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.