Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

ZOMACTON 10 mg/ml

Powder and solvent for solution for injection in prefilled syringe
(Somatropin)

FR/H/16/04/ MR

Applicant: FERRING S.A.S

Date of the PAR: February 2009

Information about the initial procedure:

Application/Legal Basis	*Full dossier 8(3)*
Active substance	Somatropin
Pharmaceutical form	Powder and solvent for solution for injection in prefilled syringe
Strength	10 mg/ml
Applicant	Ferring S.A.S
EU-Procedure number	FR/H/16/04/MR
End of procedure	*24/10/2008*

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for Zomacton 10 mg, powder and solvent for solution for injection, from Ferring S.A.S. on October, the 24th, 2008.

The product is indicated for:
- the long-term treatment of children who have growth failure due to inadequate secretion of growth hormone (GH);
- the long term treatment of growth retardation due to Turner's syndrome confirmed by chromosome analysis.

A comprehensive description of the indications and doses is given in the SPC.

Zomacton 10mg is a line extension of Zomacton 4 mg, powder and solvent for solution for injection, with a different concentration of somatropin and different solvent (metacresol). Zomacton 10 mg is presented as a sterile lyophilised powder for injection and solvent (0.33% metacresol solution in water for injections). After reconstitution the product is administered as an aqueous solution. The product should be administered subcutaneously either via a conventional syringe or through a needle-free injection device (ZomaJet VisionX). That new mode of administration is called transjection. The smaller transjection volume may lead to a decreased discomfort and improve compliance. However the higher concentration and the use of metaresol as preservative may cause local intolerance reactions.

No new systemic toxicology studies were conducted, which is acceptable as this is a line extension of a well known product. However, as the higher concentration and the use of metacresol as preservative may cause local intolerance reactions, and as Zomacton 10mg is also intended to be administered by the ZomaJet Vesion X system, two non-clinical tolerance studies were submitted.

No new clinical efficacy studies were conducted, which is acceptable as this is a line extension of a well known product. Thus, in support of this application, the applicant has submitted a pharmacokinetic (PK) and pharmacodynamic (PD) study performed in healthy adults comparing the three forms of Zomacton: Zomacton 4 mg administered with syringe and needle, Zomacton 10 mg/ml administered with syringe and needle, and Zomacton 10 mg/ml administered by ZomaJet Vision X. In addition, an observational study of local tolerability of Zomacton 10 mg/ml needle-free administered by ZomaJet Vision X was performed in children.

A Marketing Authorisation was initially granted for Zomacton 10 mg in France on June, the 15th 2006. Then, a Mutual Recognition (MRP) was initiated throughout Europe, that started on January, the 9th, 2007 and ended on October, the 24th, 2008, with France acting as Reference Member State (RMS). The Concerned Member States (CMS) involved in this procedure were Austria, Belgium, Denmark, Finland, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden and United Kingdom.

During the MRP, a potential serious risk to public health concern was raised by one CMS, about bioequivalence between Zomacton 10mg, powder and solvent for solution for injection, injected with ZomaJet device (needle-free) and Zomacton 4mg. Several questions related to the choice and acceptance criteria of the Confidence Interval for the Cmax parameter in the pharmacokinetic study, widened to 75-133% (instead of 80-120%) as required by the Guideline EMEA/CHMP/EWP/40326/2006)were raised to the applicant. The consequences of such choice on the efficacy and safety profile of Zomacton 10mg were raised. As all questions were adequately answered by the applicant, the MRP procedure ended positively and a Marketing Authorisation (MA) was granted for Zomacton 10mg, powder and solvent for solution for injection by all CMS.

A post-approval study related to the long term local tolerability in children was however asked as a commitment to the applicant.

2. QUALITY ASPECTS

2.1 Introduction

This is a new application for a line extension of the approved product Zomacton 4 mg, powder and solvent for solution for injection, as referred to in annexe II of Regulation 1084/2003. This line extension concerns the addition of new 10 mg strength of Zomacton. Both products are somatropin-containing freeze-dried powder for injection supplied with solvent for reconstitution. There are no changes of indications for the new dosage strength.

The active substance is exactly the same as for Zomacton 4 mg. Therefore, this assessment report deals mainly with the drug product part.

2.2 Drug substance

The active substance, somatropin, is exactly the same as for Zomacton 4 mg. Somatropin is produced in a strain of E. coli by insertion of the hGH gene. The manufacturing process is well established. It consists of fermentation and harvest of hGH producing *E. coli* cells, purification and lyophilization. The specification of active substance was based on Ph.Eur Monograph on Somatropin for injection.

2.3 Medicinal product

The drug product is a sterile lyophilised powder for solution for injection. The powder contains 10 mg somatropin, Mannitol, and Disodium phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate. The powder should be reconstituted with sterile solvent containing 0.33 % m-cresol in water for injections.

Composition, manufacturing process and primary packaging were adapted for the new product Zomacton 10 mg. Besides the increase amount of protein per container, new excipients of the powder and solvent have been added as compared to Zomacton 4 mg.

The powder manufacturing process includes formulation, sterile filtration/aseptic filling and lyophilisation processes. Basically, the manufacturing process was carried out according to current procedures used for the manufacture of the available commercial presentations.

The process was appropriately validated.

The specification of drug product was based on Monograph on parenteral preparation in force at the time of initial submission.

The shelf-life claimed for the powder drug product before reconstitution is 3 years at 2-8°C. The reconstituted solution can be used for multiple injections over a time period of up to 28 days at 2-8°C.

Based on stability data of the powder at 2-8°C (36 months available data) and after reconstitution (28 days at 2-8°C) a shelf life of 3 years and 28 days post-reconstitution at 2-8°C can be granted. However, considering that the shelf-life of the solvent is 2 years at 2-8°C and that the solvent is supplied with the powder in the secondary packaging, only a 2 year-shelf-life is applicable for the final product (powder and solvent). The stability data of the solvent support a shelf-life of 2 years at 2-8°C.

As for Zomacton 4 mg, reconstituted solution should be administered for subcutaneous use by using a needle free device or alternatively a conventional syringe. The device must be connected to the vial containing the solution via a spike-adapter. The compatibility of the product with the injection device has been established.

3. NON-CLINICAL ASPECTS

No new systemic toxicology study has been performed, which is acceptable for this line-extension of a well known product.

Section 5.3 (Pre clinical safety data) adequately reflects the pre-clinical data on this compound. In summary, there was no evidence of drug-related toxicity in single dose toxicity studies performed in rats, dogs as monkeys, at doses corresponding to 50-100 fold of the human therapeutic dose. No relevant toxicological signs were observed in repeated-dose toxicity studies performed in rats during 30 days. As genetically manufactured somatropin is identical to endogenous human GH, has the same biological properties, and is usually administered in physiological doses, it was not deemed necessary to perform a full range of reproductive, mutagenic and carcinogenic studies, which is acceptable. A mutagenicity study showed the absence of mutagenic potential.

However, as Zomacton 10mg is to be administered with Zomaject Vision X, a needle-free system or with an ordinary syringe, two additional non-clinical studies of the local tolerance were performed in animal models with both systems of injection.

In a *single dose study* performed in six pigs, the local tolerance of Zomacton 10mg was compared to a reference solution administered subcutaneously into their back. Local skin reactions at the injection sites were performed within 1, 2, 24, 48 and 72 hrs after subcutaneous treatment. Under the conditions of this study, injection of Zomacton 10mg or the reference solution by hypodermic needle or automatic injector system did not result in any morphological evidence of toxicity at the injection sites. In this study, the few changes (swelling and coloration) recorded were considered unrelated to treatment and they were similar after injection by hypodermic needle or automatic injector (needle-free device).

Another 28-days local tolerance study after daily administration of Zomacton 10mg with the Zomaject Vision X system was performed in twelve pigs: six juvenile (6 weeks) and six young (3 months old) pigs. The juveniles were treated with 1.0 mg Zomacton 10mg per day, while the young pigs were treated with 2.0mg per day. Dose volumes of 0.1 and 0.2 ml, respectively, were delivered using the ZomaJet 2 Vision device. A separate site was treated with the vehicle alone, using the same device and dose volumes. Treatment with Zomacton 10mg at daily doses of 1 mg (juvenile pigs) or 2 mg (young pigs) resulted in swelling and red coloration at the injection site immediately after administration. In general, swelling and coloration disappeared within 24 hours. Microscopically, treatment with vehicle and Zomacton 10mg was found to cause various slight effects that were considered to be physical reactions to administration using the ZomaJet Vision 2 device. Hyperkeratosis and serous atrophy seen only in young animals treated with Zomacton 10mg were considered to be related to the higher dose volume used in these animals. The overall assessment of these data indicates that the use of ZomaJet Vision 2 device increases local effects with both vehicle and Zomacton 10mg.

However, in conclusion it was assessed that doses of Zomacton 10mg administered by automatic injector of up to 2.0mg, i.e. the highest dose tested, were well tolerated for short term use. The majority of the macroscopic and microscopic changes were attributed to the anticipated physical effects of the dose administration with the automatic injector.

4. CLINICAL ASPECTS

4.1. Introduction

As all clinical data concerning this product have been already evaluated for Zomacton 4mg, this application essentially consists in the demonstration of the bioequivalence (on PK and PD parameters)

between Zomacton 4mg and the extension dosage Zomacton 10mg. Thus, no efficacy study was required.

Zomacton is a trade name for the recombinant human growth hormone: somatropin and is identical to the endogenous form of the pituitary human growth hormone. Zomacton is expected to produce the same pharmacological effects as the endogenous growth hormone.

Two clinical studies have been performed with Zomacton 10 mg/ml:

- a bioequivalence study (FE 999905 CS001) in healthy adults to compare three forms of Zomacton : Zomacton 4 mg/ml with syringe and needle versus Zomacton 10 mg/ml with syringe and needle versus Zomacton 10 mg/ml without needle by ZomaJet Vision X, concerning pharmacokinetic parameters and pharmacodynamic aspects;

- an observational (study FE 999905 CS002) of local tolerability of Zomacton 10 mg/ml needle-free by ZomaJet Vision X in short children.

4.2 Discussion on the clinical aspects

Efficacy

The efficacy of Zomacton 10 mg/ml needle-free is extrapolated from the efficacy of the reference Zomacton 4mg/ml**.** To bridge the similarity of the efficacy between both applications, a bioequivalence study comparing PK and PD parameters was performed between Zomacton 4mg and Zomacton 10mg (for details, see section 4.3. of the present report).

Safety

The safety profile of Zomacton 10 mg/ml needle-free including local tolerability was assessed in two studies:

1. A single dose *bioequivalence study (FE999905CS001)* performed in 24 adults. In the bioequivalence study, the good tolerance tested on the abdomen should have been checked on other sites (buttocks, legs) in adult volunteers before using the new Zomacton (with metacresol). Overall, in this study, after a unique sub-cutaneous administration, the local tolerance of the 3 formulations was good. It has to be pointed out that in this study all adults were Caucasian whereas the drug will be given to different ethnic groups. Black or Asiatic skins may react in a different way to the preservative (metacresol) included in Zomacton Vision X. A minimal back flow was noticed in 2 subjects only with the new device Zomajet Vision X (needle-free). Even if limited it might represent active substance loss and need to be further investigated. However this was not observed in the local tolerability study performed in children.

2. A repeated daily dose *tolerability study (FE999905CS002)* performed in children. This study was an open-label, non-comparative, and multicentre, phase III study performed during 12 weeks in 27 children or teenagers between the ages of 3 to 17 years, having GH deficiency or Turner's syndrome. The dose of Zomacton 10mg administered with Zomajet Vision X ranged from 0.17 to 0.23 mg/kg/week for GH deficiency and was 0.33 mg/kg/week for Turner's syndrome. The dose was adjusted for each child according to the local practice. The local tolerance was evaluated by a local investigator at each visit, and photographs were taken for central assessment by a single dermatologist. Pain and itching were evaluated by children. One subject out of 27 was withdrawn as a result of an unacceptable transjection-related site pain. 26 subjects completed the study.

In the assessment of immediate tolerability reactions (i.e. reactions occurring in the 60 minutes after dosing), "*punctual haemorrhage*" and "*redness*" were more frequent than diffuse dermal swelling according to both assessments (local and central). Results of the "*subject assessment of pain and itching*" showed that Zomacton 10 mg administered by ZomaJet Vision X was well tolerated in the majority of subjects. The proportion of subjects experiencing no pain increased by visit: 63% at the first visit, 66.7% at 2 weeks and 76.9% at 6 weeks. There was no histamine-related reaction. During this 12-week study, there was no lipodystrophy, no dermal atrophy and no sclerosis.

4.3 Pharmacokinetics: Bioequivalence Study FE 999905 CS001

This bioequivalence study was an open label, three-treatment, three-period, six-sequence, single dose, balanced crossover study with a wash-out period of 7 days between administrations performed in 24 adult volunteers. They received 1.67 mg (equivalent to 5IU) during each period. In this study, the following modalities were compared:
A. The current Zomacton 4 mg (12IU) injected by subcutaneous route with the conventional syringe (Reference treatment).
B. The new Zomacton formulation 10 mg (30IU) injected by subcutaneous route with the conventional syringe (Test 1 treatment).
C. The new Zomacton formulation 10 mg (30IU) injected by subcutaneous route with ZomaJet, the needle free device (Test 2 treatment).

The new formulation of Zomacton could be considered bioequivalent to the current formulation when both products are administered by subcutaneous route with conventional syringe, as for $AUC_{0-\infty}$ and Cmax, the 90% confidence interval lie within an acceptance range of 0.80 to 1.25. The AUC is supposed to be the main parameter for growth result in GH deficient children. Additionally to the classical PK approach, the applicant has provided a pharmacodynamic (PD) investigation based on Insulin-Like Growth Factor 1 (IGF-1) and Free Fatty acid (FFA) AUC and Cmax analysis.

Results show that when the new dosage strength solution is injected with the ZomaJet device, a higher absorption rate is observed, comparatively to the current solution. A mean 21% increase of Cmax is observed with a 90% confidence interval (CI) of (116%; 132%). This CI is not in line with what is required by the Guideline that do not lay within acceptance range; but the 90% CI for $AUC_{0-\infty}$.([106; 116]%) is in line with the Guideline. Results show that similar AUC and Cmax were obtained with the three modalities described above for IGF1 end FFA.

Discussion. The design of that study is considered adequate. The wash-out period of 7 days is long enough to avoid any carry over effect to the second or third period. The outcome of the study shows that sufficient number of subjects was included in the study. The analytical method was satisfactory validated (pre-study and within study). The statistical methods were adequately described and are acceptable and there are no major protocol deviations.

Based on the submitted bioequivalence study, the Zomacton 10mg could be considered bioequivalent to the current Zomacton 4mg when these products are administered by subcutaneous route with a conventional syringe. When administered with ZomaJet device (needle-free), the bioequivalence between both forms was confirmed with respect to AUC but not for Cmax, a slightly higher increase in Cmax being observed. This difference was not considered to be clinically relevant. Moreover, the pharmacodynamic investigations based on IGF1 profile did not evidence any significant difference between the products under consideration.

5. OVERALL CONCLUSION

Considering the extensive knowledge on the preclinical data for somatropin and the identical safety profile of Zomacton 4 mg and Zomacton 10 mg, it can be stated that Zomacton 10 mg does not raise any new preclinical concerns.

Based on the submitted data, the bioequivalence between Zomacton 10 mg/ml needle-free and the reference product Zomacton 4mg with syringe and needle was demonstrated. Therefore the same effect on growth in children can be expected.

The tolerance of the device analysed in 24 healthy volunteers and in 26 paediatric patients was good. Long term local tolerability with the new system were however required.

No risk management plan has been proposed by the applicant. When the MRP procedure started, Zomacton 10 mg had a marketing authorization but was not available on the French market, therefore the RMS had wished a follow-up measure (FUM) to assess local tolerability during one year in

children of different ethnic origins, as clinical experience was limited to 50 subjects only, who have been exposed to the new formulation of Zomacton with a new strength and the needle-free device during clinical trials. Zomacton 10 mg/ml has been available in France since June 2008. In the period from 12 June 2008 until 31 August 2008, 273 boxes (pack size of 1) have been sold in France. No side or adverse events have been reported to the applicant about Zomacton 10 mg/ml until 26 September 2008.

Following this MRP, the RMS and CMS agreed that the applicant should perform a long-term local tolerability as a commitment. Therefore, a post-marketing study FE 999 905 CS007 is planned. The treatment period will be 12 months; 60 patients will be treated with Zomacton 10 mg/ml using the needle-free injection device Zomajet Vision X. Local tolerability will be assessed at every study visit.

During the MRP procedure, several changes have been made in the SPC and in the Package Leaflet. In the SPC, in section 4.4, additional wording was included to point out that the local tolerability study before marketing authorization only included Caucasian children and lasted 12 weeks. In the Patient Leaflet, illustrations for preparation of the product with both systems: with the needle-free device or with a conventional syringe were added. For the MRP, a readability test of the patients leaflet has been performed in English language. The user testing was deemed acceptable.

In conclusion, Zomacton 10mg/ml is authorized in all concerned member states with a post-marketing commitment to assess long-term local tolerability of Zomacton 10mg/ml using the needle-free injection device ZomajetVisionX in children of different ethnic groups.

The Member States mutually recognised the French evaluation of the marketing authorisation.