European Medicines Agency
Evaluation of Medicines for Human Use

London, 22 January 2009
Doc. Ref.: EMA/356718/2010

CHMP ASSESSMENT REPORT
FOR
COZAAR and associated names

International Nonproprietary Name:
irbesartan

Procedure No. EMEA/H/A-29 PAD/1022

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

Pursuant to Article 29 of Regulation (EC) No 1901/2006, as amended, and Annex II (point 2(iv)) of Regulation 1084/2003, Merck Sharp & Dohme BV submitted to the EMEA on 23 May 2008 an application for a new pharmaceutical form associated with a new strength for the above mentioned medicinal product.

The application concerns powder and solvent for oral suspension 2.5 mg/ml.

Merck Sharp & Dohme BV is the Marketing Authorisation Holder for Cozaar and associated names film-coated tablets which was included in the list of products for Product Information harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of the Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SPCs and therefore to harmonise these divergent SPCs across the European Union.
Following the Art 30 Referral Procedure the European Commission has adopted a decision amending the marketing authorizations for Cozaar and associated names on 3 September 2008.

Licensing status:
Cozaar and associated names are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom as well as in Iceland and Norway.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

- Rapporteur: Pieter A. de Graeff
- Co-Rapporteur: Harald Enzman

Paediatrics
Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMEA Decision on a Paediatric Investigation Plan (PIP) – (Decision P/9/2008) issued on 29 February 2008. The PIP is not yet completed and the application contained only the paediatric results collected in accordance with the Measure 1 of the agreed PIP (Decision P/9/2008) which is related to age appropriate liquid formulation subject of the applied dossier. The PDCO (Paediatric Committee) has performed the compliance check with the Measure 1 of the agreed PIP and issued a Report on 8 May 2008 confirming compliance with the completion of the Measure 1.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hypertension is an important risk factor for cardiovascular morbidity and mortality and occurs in 1 to 10 % of children and adolescents. The concern is growing about the possible relationship between blood pressure patterns in youth and the subsequent development of adult essential hypertension. Guidelines have been established for control of blood pressure in children and urged better detection and control of hypertension in children. Treatment options are less clearly defined. For essential hypertension, non-pharmacologic therapy such as weight reduction and exercise are first choices. Pharmacological interventions include angiotensin converting enzyme inhibitors (ACEI), angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, diuretics. Although the number of compounds in each class with established doses for pediatric patients is growing, there is still not enough option for regimens customized to the individual needs of a patient.

The pediatric program for Losartan was designed to investigate pharmacokinetics, appropriate dosage and clinical efficacy and safety in pediatric patients and included subjects between 6 and 16 years of age. Younger patients were included in the pharmacokinetic investigation.

This submission concerns a line extension for an age appropriate liquid formulation. The clinical studies supporting this application have been assessed in the framework of the Art 30 Referral Procedure, which triggered in order to harmonize the SPC across the European Union.

2.2 Quality aspects

Introduction

The application concerns powder and solvent for oral suspension 2.5 mg/ml. The product is presented as sachets containing powder, which is to be suspended in the liquid vehicle to form a multi-dose oral suspension.
Each sachet contains 500 mg of losartan (as potassium salt), which after dispersion in 200 ml of suspending vehicle (Ora-Blend SF) gives a suspension with final concentration of 2.5 mg/ml. The powder, besides the active substance, contains the following excipients microcrystalline cellulose, pregelatinized starch, lactose hydrous, magnesium stearate and colorant Opadry White composed of hypromellose, hydroxylpropylcellulose and titaniumdioxide.
A suspending vehicle Ora-Blend SF is commercially available, and it is composed of antifoam emulsion, microcrystalline cellulose, carboxymethylcellulose sodium, anhydrous citric acid, purified water, xanthan gum, methylparaben, propylparaben, sodium phosphate monobasic monohydrate, potassium sorbate, carrageen, calcium sulphate trisodium phosphate, Berry Citrus Sweet Flavouring, glycerine, sodium citrate anhydrous, sodium saccharin, and sorbitol solution.

Cozaar and associated names powder and solution for oral suspension will be supplied as a kit, which consists of the following components:

- sachet with powder for oral suspension
- suspending vehicle - Ora-Blend SF
- empty amber polyethylene terephthalate (PET) bottle with child resistant closure
- push in bottle adaptor (PIBA)
- dosing syringe

Prior dispensing the product to patients powder should be mixed with the suspending vehicle in the amber polyethylene terephthalate (PET) bottle, by pharmacist to obtain an extemporaneous, multi-dose oral suspension 2.5 mg/ml.

Active Substance

The active substance used in the proposed formulation is identical with the one used in the manufacture of the approved Cozaar and associated names film-coated tablets, which are marketed across EU.

Medicinal Product

- Pharmaceutical Development

The objective of formulation development was to provide an age appropriate liquid formulation of losartan potassium that is bioequivalent to currently marketed tablets. The formulation should also fulfil requirements of the Measure 1 from the decision on the PIP. The PDCO requested a commercial liquid formulation as an age appropriate pharmaceutical form with the remark that only in case of sound justification that a commercial liquid formulation cannot be developed, the applicant should develop a dry powder in sachet for in-situ reconstitution as a suspension where the powder for reconstitution and the vehicle must be made available in the same packaging (as a kit).
The choice of powder for oral suspension has been justified as more suitable product than oral disintegrating tablet or oral solution, due to extreme bitter taste, or chewable tablet and oral powder, due to dosing problems (no dosing flexibility), or ready suspension, due to unacceptable changes during storage. Relevant evidence that it was not possible to develop a commercial oral suspension due to observed significant changes in the dissolution profile has been provided. Also presence and choice of preservative system has been justified. Presence of Opadry White in the powder formulation is important to achieve acceptable dissolution on storage of the oral suspension.

The starting point in the development program was tablet formulation. The proposed powder for suspension consists of a pre-compression tablet blend with coating components. Initially, the proposed powder was composed of uncompressed tablet blend without coating components. Suspensions prepared from this powder were placed on stability and exhibited increasingly poor dissolution over a four-week study. An investigation of the dissolution behaviour identified that the addition of Opadry White improved the dissolution of the suspension on stability. The reason for this is that the components of Opadry White, specifically hypromellose, hydroxylpropylcellulose, are known to provide steric stabilization of media milled dispersions and minimize Ostwald ripening effects. Based on the results Opadry White was included in the formulation.

The proposed powder (when compared to e.g. granulate) has limited flow conditions and shows selective adsorption of the active substance to the inner surface of the sachet, resulting in the need of an overfill of 6.5 % and the requirement to prepare the suspension uniquely in pharmacies with a specific instruction not to rinse the sachet. However, development, validation and stability studies have certified sufficiently that the product is acceptable from chemical-pharmaceutical point of view.
The pH of the prepared suspension ensures minimal solubility of the active substance. This approach is suitable for taste masking. Bitterness has also been corrected with flavours, saccharin and sorbitol. The choice of a suspension is therefore justified.
Extemporaneous suspensions prepared from the currently marketed tablets containing 50 mg of losartan potassium and powder for oral suspension 500 mg, were subjected to multimedia dissolution testing to compare the profiles generated in each media. In every medium tested, greater than 85% dissolution was achieved in less than 5 minutes, indicating that both suspensions are fast dissolving and all profiles are visually similar.

- Adventitious Agents

Among excipients used in the medicinal product only lactose is of the animal origin. Declarations from suppliers of lactose were provided stating that lactose is produced from milk sourced from healthy animals and is collected in the same manner as milk for human consumption, and is not prepared with the use of other ruminant materials with the possible exception of calf rennet.

- Manufacture of the Product

The manufacturing process of the powder for oral suspension is based on the approved manufacturing process of tablets. Losartan potassium, microcrystalline cellulose, lactose hydrous, and pregelatinized starch are added through a screen into a suitable blender and mixed. Magnesium stearate is added through a screen to the powder mix, followed by mixing in a suitable blender. A portion is extracted from the parent batch and blended with Opadry White. Once blended, the resulting powder is filled into sachets.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

Process validation was carried out on three batches and showed that the powder for suspension can be manufactured reproducibly according to the finished product specifications.

- Product Specification

The proposed specifications include tests for appearance, identity (HPLC and TLC), assay (HPLC), content uniformity (HPLC), impurities (HPLC) and bioburden. The specification covers basic parameters for a powder for suspension. Identity is tested by a combination of TLC and HPLC comparison of the retention values of the sample and the reference standard. Specification for impurities includes known impurities individually specified and any other impurities. Assay is conventionally specified and content uniformity according to Ph. Eur. Microbial purity is tested on a periodic basis.

Test for an assay, impurities, content uniformity and identity is performed using the same analytical HPLC method. The HPLC method has been satisfactorily validated with regards to specificity, linearity, accuracy, precision and robustness.

The suspending vehicle (Ora-Blend SF) is considered a relevant part of the medicinal product as stability, preservation, re-suspendability, speed of sedimentation, viscosity, taste, deliverable volume, uniformity of content of dose are critical for product quality depend on the quality of the vehicle. Therefore the medicinal product specifications for powder for oral suspension also include tests and acceptance criteria for suspending vehicle (Ora-Blend SF). The proposed specifications include tests for appearance, identity of preservatives (HPLC), assay of preservatives (HPLC), pH, specific gravity, and microbiological purity.

Batch analysis data on three commercial scale (process validation) batches of the medicinal product confirmed consistency of the manufacturing process. All results comply with specifications.

Powder for oral suspension will be packaged in an aluminium foil sachet. Suspension will be prepared and stored in polyethylene terephthalate (PET) bottle with a child resistant closure. A calibrated oral syringe and a press-in bottle adapter (PIBA) are included in a kit for dosing of the suspension. The oral syringe consists of three components, which include the oral dispenser barrel, the plunger rod, and an O-ring. The barrel is lubricated with silicone fluid. The oral dispenser barrel is composed of polypropylene and is lubricated with silicon fluid. The plunger rod is also composed of polypropylene and includes a white colorant. O-ring is moulded from silicone.

- Stability of the Product

Stability data generated for 3 batches of the powder for oral suspension in the proposed packaging, stored for 6 months and initial stability data for a fourth bridging batch stored 3 months under normal conditions (25 °C/65 % RH) and accelerated conditions (40 °C/75 % RH) have been provided. In addition stability data generated for the tablets have been submitted as supportive results as formulation of the powder for oral suspension is equivalent to the marketed tablets. The stability

results indicate satisfactory stability of the product at both the long term and the accelerated storage conditions. No significant changes were observed at any storage condition.

Stability data supporting proposed shelf life of the suspending vehicle (Ora-Blend SF), generated during storage under long term (25°C/60% RH) and accelerated (40°C/75% RH) storage conditions have also been provided.

In use stability for three pilot scale batches have been performed. The obtained results support proposed in-use shelf-life of the reconstituted oral suspension. The photostability studies showed that there was no difference between the stability of the oral suspension in open dish and the control sample kept in dark.

Discussion on chemical, pharmaceutical and biological aspects

From chemical-pharmaceutical point of view the starting point of the development program of the formulation applied for is not understood and does result in several limitations to the quality of the product. Development started from the tablet formulation and resulted in a powder for suspensions that is a pre-compression tablet blend with coating components. This powder (when compared to e.g. granulate) exhibits limited flow conditions and shows selective adsorption of the active substance to the inner surface of the sachet. However, development, validation and stability studies have proven sufficiently that the product can be reproducibly manufactured and in its quality overall is acceptable. The excipients used in the preparation of the medicinal product and manufacturing process selected are standard ones.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed time-frame.

2.3 Non-clinical aspects

Suspending vehicle (Ora-Blend SF) contains preservatives, including propylparaben. This excipient, according to food legislation (Directive 2006/52/EC of the European Parliament and of the Council of 5 July 2006 amending Directive 95/2/EC on food additives other than colours and sweeteners and Directive 94/35/EC on sweeteners for use in foodstuffs) should not be used in the dietary products. Therefore additional evidence proving safety of this excipient was provided.

Ora-Blend SF contains 0.029 % w/w methylparaben and 0.004 % w/w propylparaben. Assuming a maximum daily dose of 50 mg losartan, the maximum daily intake of methylparaben will be 5.8 mg and 0.8 mg of propylparaben.

According to the published literature data there is a potential risk of reprotoxicity on male fertility, identified in the juvenile male rat given propylparaben orally. After per os administration to juvenile male Wistar rats for duration of 4 weeks, propylparaben showed effects on spermatogenesis (reduction in the testicular and epididymal quantity of spermatozoa) with a LOAEL of 12.4 mg/kg, and reduction of serum testosterone concentrations with a NOAEL of 125 mg/kg. The mechanism seems to be an effect of propylparaben on hormonal homeostasis (disturbance of the hypothalamo-hypophysiary system, local oestrogenic action), and the modification of testosterone plasma concentrations seems to be secondary to a deterioration of spermatogenesis, which occurs at lower doses of propylparaben. No effects of propylparaben on sexual maturation (i. e. no alterations of the weights of sexual organs like testis, epididymis, prostate, seminal vesicle) were induced by propylparaben. The reversibility of the reprotoxic effects and a NOAEL for propylparaben have not been determined; furthermore, the 4 weeks duration of the study performed in juvenile rats covers only half of a cycle of spermatogenesis (a cycle lasts for 48 – 52 days in rats and for 64 – 72 days in humans). Assuming that the NOAEL is not much lower when compared to the LOAEL and taking the usual safety factor of 100 into account, a value for the PDE of about 100 µg/kg can be calculated. Therefore maximum daily intake of 0.8 mg propylparaben achieved with per os administration of the proposed formulation is low. For methylparaben, no reprotoxic effects were observed in juvenile rats up to per os doses of 1030 mg/kg after 8 weeks treatment, and the ADI (acceptable daily intake) is 10 mg/kg/day, which is much higher

when compared to the methylparaben intake after the administration of the proposed formulation (maximum 5.8 mg/day).

In conclusion concentrations of methylparaben and propylparaben present in the proposed formulation do not cause a reprotoxic risk. Propylparaben is present in many marketed medicinal products and as long as no final statement could be reached about the safety of propylparaben no action should be taken against any existing product, while new products with parabens included, should be accepted only if the concentration and expected human dose will not be different from the "usually" accepted products. The amount of propylparaben in the proposed formulation is lower than usually used in standard formulations.

2.4 Clinical aspects

The clinical studies supporting this application have already been assessed in the framework of the pediatric worksharing procedure and the conclusions adopted in the CHMP opinion on the art 30 Referral. A harmonized text for the use of Cozaar and associated names in children has been agreed upon as part of this exercise.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.5 Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system as described by the applicant is of good quality and is in line with section 2.2 of the Volume 9A of "The Rules Governing Medicinal Products in the European Union" and fulfils the legislative requirements.

Risk Management Plan

Concerning the need for a risk management plan the MAH declared that no such plan is deemed necessary, which is considered to be in accordance with the Guideline on Risk Management Systems for Medicinal Products for Human Use as it is an application for a new pharmaceutical formulation and no new paediatric population will be exposed to the product after the approval (therapeutic indications will not be changed with this application). However, in view of the population that will use Cozaar and associated names powder and solution for oral suspension it is imperative that the applicant will closely monitor the paediatric patients after approval. Routine pharmacovigilance is accepted; however, safety data should be presented in the PSUR separated by age group and used formulation (e.g. tablets or oral suspension).

PSUR should be submitted every 6 months for a year. After that year the safety data will be evaluated and it will be decided whether a longer PSUR period is permitted.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

From chemical-pharmaceutical point of view the starting point of the development program of the formulation applied for is not understood and does result in several limitations to the quality of the product. Development started from the tablet formulation and resulted in a powder for suspensions that is a pre-compression tablet blend with coating components. This powder (when compared to e.g. granulate) exhibits limited flow conditions and shows selective adsorption of the active substance to the inner surface of the sachet. However, development, validation and stability studies have proven

sufficiently that the product can be reproducibly manufactured and in its quality overall is acceptable. The excipients used in the preparation of the medicinal product and manufacturing process selected are standard ones.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

Concentrations of methylparaben and propylparaben present in the proposed formulation do not cause a reprotoxic risk.

Clinical

The clinical studies supporting this application have already been assessed in the framework of the pediatric worksharing procedure and the conclusions adopted in the CHMP opinion on the art 30 Referral. A harmonized text for the use of Cozaar and associated names in children has been agreed upon as part of this exercise.

Risk-benefit assessment

The risk/benefit is considered acceptable even though from chemical-pharmaceutical point of view the starting point of the development program of the formulation applied for is not understood and does result in several limitations to the quality of the product. The powder (when compared to e.g. granulate) exhibits limited flow conditions and shows selective adsorption of the active substance to the inner surface of the sachet. However, development, validation and stability studies have proven sufficiently that the product can be reproducibly manufactured and in its quality overall is acceptable. The excipients used in the preparation of the medicinal product and manufacturing process selected are standard ones and safety aspects with their use have been sufficiently explained and proven.
The choice of powder for oral suspension has been justified as more suitable product than oral disintegrating tablet or oral solution, due to extreme bitter taste, or chewable tablet and oral powder, due to dosing problems (no dosing flexibility), or ready suspension, due to unacceptable changes during storage. Relevant evidence that it was not possible to develop a commercial oral suspension due to observed significant changes in the dissolution profile has been provided. Also presence and choice of preservative system has been justified.

Recommendation

Based on the CHMP review of data on quality, the CHMP considered by consensus decision that the risk-benefit balance of Cozaar and associated names in the treatment of

- essential hypertension in adults and in children and adolescents 6 - 16 years of age.
- renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment
- chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40 % and should be stabilised under the treatment of the chronic heart failure
- reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG was favourable and therefore recommended the granting of the marketing authorisation.

was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP took note that the PIP is not yet completed. Only the measure 1 of the PIP (Decision P/9/2008) related to age appropriate liquid formulation is completed and compliant. The

paediatric data related to the age appropriate liquid formulation subject to this application are reflected in the Summary of Product Characteristics, Package Leaflet and labelling of the pharmaceutical form concerned. Compliance with the remaining PIP measures in accordance with the agreed timelines must be checked when the PIP is completed.