Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

ENALAPRIL HCTZ TEVA PHARMA 20mg/12.5 mg, scored tablets

Enalapril maleate & Hydrochlorothiazide

FR/H/309/01/MR

Applicant: TEVA PHARMA B.V.

Date of the PAR: October 2007

Information about the initial procedure:

Application type/Legal basis	Generic application 10(1)
Active substance	Enalapril maleate& Hydrochlorothiazide
Pharmaceutical form	Scored tablets
Strength	20 mg/12.5 mg
Applicant	TEVA PHARMA B.V.
EU Procedure-number	FR/H/309/01/MR
End of procedure	01/02/2007

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for ENALAPRIL HCTZ TEVA PHARMA 20 mg/12.5 mg, scored tablets from TEVA PHARMA B.V on 11/10/2005.

The product is a fixed combination, indicated for the treatment of essential hypertension, in patients who cannot be treated adequately with monotherapy with enalapril as a single agent, and in patients who have already been stabilised by the individual active substances given in the same proportions.

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

The generic application for marketing authorisation concerns ENALAPRIL HCTZ TEVA PHARMA 20 mg/12.5 mg, scored tablets.

The medicinal product is claimed to be essentially similar to Co-Renitec 20 mg/12.5 mg, scored tablet marketed in France by Merck Sharp & Dohme Chibret.

The Applicant has submitted a bioequivalence study. The reference product used in the bio-equivalence study is Innozide® (20 mg/12.5 mg, tablets) marketed by MSD in the UK.

No new preclinical or clinical studies were conducted, which is acceptable for this kind of application

During the procedure, “potential serious risk to public health” concerns related to bioequivalence study and to the SPC were raised.
At day 90, the application was referred to the CMD referral due to persistence of major objections relative to the therapeutic indications and to the posology in elderly.

2. QUALITY ASPECTS

2.1 Introduction

ENALAPRIL HCTZ TEVA PHARMA is presented in the form of white round scored tablets containing 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide.
The excipients are lactose monohydrate, maize starch, starch pregelatinised, sodium hydrogeno carbonate and magnesium stearate.
The medicinal product is packed in oriented polyamide (OPA) / Alu / PVC – Aluminium blister pack.

2.2 Drug substance

Both Drug substances Enalapril maleate and Hydrochlorothiazide have a monograph in the Ph.Eur. The Quality of the two active substances: Enalapril Maleate from Esteve Quimica and Hydrochlorothiazide (HCTZ) from Pliva are covered with the CEP procedures

Enalapril maleate is controlled by TEVA according to Ph Eur 1420 monograph and additional in-house methods for residual solvents and particle size
Enalapril maleate is a white crystalline powder, sparingly soluble in water.

Hydrochlorothiazide (HCTZ) is controlled by TEVA according to Ph Eur 394 monograph with additional in-house methods for particle size.
Hydrochlorothiazide is a white, crystalline powder very slightly soluble in water.

Both active substances specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated. Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

2.3 Medicinal product

ENALAPRIL HCTZ TEVA PHARMA 20 mg/12.5 mg, scored tablets, is formulated using excipients described in the current Ph Eur.

All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The development is sufficiently described in accordance with the relevant European guidelines. Comparative in vitro dissolution profiles and impurities profiles of the generic product and the reference product support the essentially similar character.

The manufacturing process has been sufficiently described and critical steps identified.
Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 2 years with special storage precautions “Do not store above 25°C”.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar to Co-Renitec which was approved based on a full application with regard to preclinical data, no further data are necessary.

4. CLINICAL ASPECTS

4.1 Introduction

Enalapril/HCTZ is a well-established combination used for the treatment of essential hypertension, in patients who cannot be treated adequately with monotherapy with an angiotensin converting enzyme inhibitor.

Its efficacy and safety in this indication have been extensively demonstrated in clinical trials and post-marketing use, which also support the recommendations of the proposed Summary of Product Characteristics.

4.2 Pharmacokinetics

The product is a generic version of Co-Renitec, which is a fixed combination of enalapril and HCTZ. The main PK characteristics of both active ingredients are briefly summarized below.

- Enalapril maleate: Enalapril maleate is a pro-drug which is activated in the liver to the pharmacodynamically potent substance "Enalaprilat" via ester cleavage (hydrolysation). Enalapril maleate is rapidly absorbed from the intestinal tract. About 50-70 % of Enalapril maleate is absorbed from gastro-intestinal tract. Oral absorption is not affected by simultaneous food intake. The accumulation half-life of Enalaprilat is approximately 11 hours. A terminal half-life of about 35 hours is observed representing the small fraction of Enalapril that is bound to Angiotensine-Converting Enzyme (ACE).
- Hydrochlorothiazide (HCTZ): HCTZ is well absorbed from gastro-intestinal tract. The reported bioavailability is of about 65-70 %. Its plasma half-life is estimated to be 5 to 15 hours.

To support the application, the applicant has submitted a bioequivalence study investigating the application product (20 mg/12.5 mg tablet) versus the brand leader in the UK (INNOZIDE®).

The study was conducted according to an open-label, two-treatment, two-period, two-sequence, single-dose cross-over design. Twenty-eight (28) plus four (alternates adult healthy male volunteers were enrolled and randomized. Two subjects were dropped out from the study (consent withdrawal for personal reasons, before dosing of period 2). A third subject withdrew after dosing of period 1 for a serious adverse reaction. Twenty eight subjects were analyzed as per protocol according to the statistical plan.

The study medication was administered in each period under fasting conditions. Each treatment was separated by a wash-out period of 21 days. For Enalapril and Enalaprilat plasma levels monitoring, 22 blood samples were collected over the 96 hours period post dosing. In order to investigate HCTZ, 17 blood samples were collected up to 36 hours post-dosing.
Plasma concentrations of bisoprolol and HCTZ were monitored in the collected plasma samples by the means of fully validated analytical techniques.
The primary PK parameters investigated in the study were: AUC0-t, AUC0-inf, Cmax and Tmax. The main findings of the study are tabulated below.

Enalapril: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range).

	Test	**Référence**		**ICS 90 %**
AUC 0-t (ng.h/ml)	**201.3 ± 61**	**195.3 ± 54.7**	**NS**	**[96 ; 110] %**
AUC 0-□ (ng.h/ml)	**202.4 ± 60.9**	**196.5 ± 54.6**	**NS**	**[96 ; 110] %**
Cmax (ng/ml)	**128.4 ± 34.8**	**118.6 ± 36.6**	**P < 0.1**	**[101 ; 121] %**
Tmax (h)	**0.8**	**0.8**	**NS**	**-------**

Enalaprilat: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range).

	Test	**Référence**		**ICS 90 %**
AUC 0-t (ng.h/ml)	**709 ± 164.5**	**693 ± 145.7**	**NS**	**[95 ; 109] %**
AUC 0-α (ng.h/ml)	**744.1 ± 168.1**	**730.1 ± 145.6**	**NS**	**[95 ; 109] %**
Cmax (ng/ml)	**80.3 ± 25.3**	**77.5 ± 25.8**	**NS**	**[95 ; 115] %**
Tmax (h)	**3.5**	**3.5**	**NS**	**-------**

HCTZ: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range).

	Test	**Référence**		**ICS 90 %**
AUC 0-t (ng.h/ml)	**469.5 ± 85.3**	**450 ± 96.2**	**NS**	**[100 ; 111] %**
AUC 0-α (ng.h/ml)	**510 ± 83.1**	**494.4 ± 97.8**	**NS**	**[99 ; 109] %**
Cmax (ng/ml)	**78.8 ± 21.6**	**75.8 ± 19.4**	**NS**	**[95 ; 114] %**
Tmax (h)	**1.8**	**2**	**NS**	**-------**

The outcome of this study demonstrated the bioequivalence of the Enalapril/HCTZ Teva to the reference product in the UK (INNOZIDE)

4.3 Discussion on the clinical aspects

The bioequivalence of the product under consideration has been established in comparison with an adequate comparator.
Taking into account the pharmaceutical characteristics of the products (an immediate release pharmaceutical form) a bioequivalence study was performed with the tablets under consideration at single dose and under fasting conditions.
As Enalapril/HCTZ TEVA 20/12.5 mg is a generic version of the already approved and well known Co-Renitec (brand leader in France), no new clinical studies were conducted and bioequivalence study could be considered as acceptable for assuming product efficacy and safety.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of ENALAPRIL HCTZ TEVA PHARMA 20 mg/12.5 mg, scored tablets is demonstrated, and it is a generic form of Co-Renitec 20 mg/12.5 mg, scored tablet which is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents (Investigation of Bioavailability and Bioequivalence).

As differences in the approved indications between Member States were highlighted during the procedure, there was a discussion in the CMD(h).
Two points were specifically discussed:

1. the therapeutic indication : addition or not, of ***patients inadequately controlled by HCTZ alone***
2. the proposed initial dose of ***half a tablet in the elderly patients with renal impairment***.

As very limited data were provided to support the indication "*in patients inadequately controlled by HTCZ alone"*, all the Member States agreed to not accept it.
Moreover, the addition of a new substitution indication was proposed and was accepted by all the Members States.

Thus, the indication finally validated is:

"This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with enalapril alone.
This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.
This fixed dose combination is not suitable for initial therapy"

Concerning the possibility of a half dose in elderly patients with renal impairment, a compromise was found during the CMD Meeting held on 23rd, January 2007 and it was accepted by all the Member States to delete this sentence in the SPC.

Finally, all the CMS mutually recognised the marketing authorisation of ENALAPRIL/HCTZ TEVA PHARMA 20mg/12.5mg, initially granted by AFSSAPS (France).

The SPC, Patient Leaflet and packaging were presented according to the agreed template.
However, a commitment was given during the MRP procedure to provide a new User testing Report, using the final Patient Leaflet accepted as per day 90.