PUBLIC ASSESSMENT REPORT

Scientific Discussion

Bisoprolol HCTZ Teva 2.5 mg/6.25 mg, 5 mg/6.25 mg & 10 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate/Hydrochlorothiazide

FR/H/307/01-03/DC

Applicant: TEVA Classics S.A.

Date of the PAR: November 2007
### 1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for **Bisoprolol/HCTZ Teva 2.5 mg/6.25 mg, 5/6.25 mg and 10 mg /6.25 mg film-coated tablets** from Teva Classics S.A. on 16/11/2007.

The product is indicated in the treatment of mild to moderate arterial hypertension.

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

The generic application for marketing authorisation concerns Bisoprolol/HCTZ Teva film-coated tablets in the strengths 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg /6.25 mg.

The medicinal products are claimed to be essentially similar to Lodoz 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10/6.25 mg film coated tablets marketed in France by Merck Lipha Santé.

Apart from an impurity profile, no new preclinical and clinical studies were conducted, which is acceptable for this kind of application.

Initially, the Applicant has submitted two bioequivalence studies performed each of them with two different reference medicinal products: Lodoz 10 mg/6.25 mg, film-coated tablets marketed by Merck Lipha Santé in France and Concor 10 plus Filmtabletten marketed by Merck Pharma GmbH in Germany.

A potential serious risk to public health concern was raised by France as RMS, and a CMD referral was initiated. A list of questions was agreed upon regarding deficiencies in clinical aspects for strengths 5 mg/6.25 mg and 10 mg /6.25 mg and in clinical and pharmaceutical aspects for strength 2.5 mg/6.25 mg.

For Bisoprolol/HCTZ Teva 5 mg/6.25 mg and 10 mg /6.25 mg film-coated tablets, the bioequivalence study of the 10 mg/6.25 mg tablet to an adequate comparator was not demonstrated. Indeed, the validity of the analytical technique employed in the study was not certain. During the CMD referral a new bioequivalence study has been submitted and approved. The CMD referral was ended positively and approval was granted by all concerned member states.

For Bisoprolol/HCTZ Teva 2.5/6.25 mg, film-coated tablets, the bioequivalence study of the 2.5 mg/6.25 mg tablet to an adequate comparator was not demonstrated. The reference product Concor 10 plus 10/25 mg was not representative of the French reference product Lodoz 2.5/6.25 mg film coated tablet and moreover the validity of the analytical technique employed in the study was not certain. During the CMD referral a relevant new bioequivalence study with an adequate comparator, Lodoz 2.5/6.25 mg film coated tablet marketed in France, has been submitted and approved.
2. QUALITY ASPECTS

2.1 Introduction

The Bisoprolol/HCTZ Teva products are presented in the form of film-coated tablets containing 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg /6.25 mg of bisoprolol fumarate and hydrochlorothiazide.

The excipients are maize starch, microcrystalline cellulose, colloidal anhydrous silica, calcium hydrogenophosphate, magnesium stearate and Opadry.

The film-coated tablets are packed in Aluminium-aluminium blister packs.

2.2 Drug substance

The Active Substance Master File (ASMF) procedure is used for the drug substance Bisoprolol fumarate. The documentation have been satisfactorily elaborated and justified in accordance with relevant guidelines.

The drug substance specification is based on the monograph for bisoprolol fumarate in USP. Bisoprolol fumarate is a white, crystalline powder soluble in water. The drug substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The proposed specifications for impurities in the active substance are in accordance with EU/ICH Q6A and Q3A guidelines. Additional in-house method for particle size is included.

The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

Hydrochlorothiazide has a monograph in the Eur. Ph. and the manufacturer holds a Certificate of suitability of the monograph. The documentation provided for this drug substance is of sufficient quality in view of the present European regulatory requirements.

Hydrochlorothiazide is a white, crystalline powder very slightly soluble in water.

The drug substance specification includes relevant tests and the limits for impurities/degradation products are tighter than in Eur. Ph. monograph. Additional in-house method for particle size is included. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

2.3 Medicinal product

Bisoprolol/HCTZ Teva 2.5 mg/6.25 mg, 5/6.25 mg and 10 mg /6.25 mg film-coated tablets are formulated using excipients described in the current Eur. Ph excepted for the film coating which is performed by a ready to use suspension.

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.
For strengths 5 mg/6.25 mg and 10 mg/6.25 mg and according to “Note for guidance on the investigation of bioavailability and bioequivalence, QWP/1401/98” bioequivalence study with strength 10 mg/6.25 mg as biobatch, has been extended to strength 5/6.25 mg. From a pharmaceutical point of view the bioequivalence study has been performed with an adequate comparator i.e. Lodoz 10/6.25 film coated tablets marketed in France.

For strength 2.5 mg/6.25 mg the demonstration of the bioequivalence between the Teva product 2.5/6.25 mg and the French reference product Lodoz 2.5/6.25 mg was not provided for France since the reference product used in the bioequivalence study was not adequate. Therefore a CMD referral was initiated. A new bioequivalence study has been submitted and approved with Lodoz 2.5/6.25 mg film coated tablet marketed in France as comparator. The CMD referral was ended positively.

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 proposed specifications for the control of the drug product are adequate. The methods are satisfactorily described and validated. The batch analysis results show that the drug product meet the specifications proposed.

The packaging is sufficient to ensure the quality of the tablets.

The conditions used in the stability studies are according to the ICH stability guideline.

On the basis of the submitted stability data, a shelf life of 18 months with the storage condition ‘do not store above 30°C’ has been granted.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Regarding the preclinical aspects, considering that this application is based on the essential similarity of the proposed product demonstrated through studies carried out to prove the similarity of its performance from various points of view: quality, safety and bioequivalence with the reference product, no additional non clinical studies were performed. Non clinical pharmacodynamic, pharmacokinetic and toxicological aspects have been studied and characterized during the development of the reference product. However, an impurity profile was carried out. Concerning the starting material “Epoxibiso”, the limit for this impurity has been tightened to 0.75µg/day in order to comply with the Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day according to the current guideline CPMP/SWP/5199/02 on the genotoxic impurities or otherwise qualified according the guideline CPMP/ICH/2737/99.

4. CLINICAL ASPECTS

4.1 Introduction

Bisoprolol/Hydrochlorothiazide (HCTZ) is a fixed combination of a β₁-selective adrenoreceptor antagonist and a thiazide diuretic. This combination is a well-established combination indicated for the
treatment of mild to moderate arterial hypertension. Its efficacy and safety in this indication have been extensively demonstrated in clinical trials and post-marketing use.

**4.2 Discussion on the clinical aspects**

As Bisoprolol/HCTZ Teva film-coated tablets is a generic version of Lodoz film coated tablets (brandleader in France), no new clinical studies were conducted and bioequivalence studies could be considered as sufficient and acceptable for assuming efficacy and safety.

The bioequivalence of the product has been demonstrated in comparison with adequate reference products.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC of the reference product Lodoz. The proposed SPC was in accordance with the presently approved French SPC for Lodoz film coated tablets. However, as a type II variation (especially related to sections 4.4 and 4.5) was ongoing for the reference product Lodoz at the time of the procedure, the applicant has committed to apply for a type II variation to update both SPC and PIL within 3 months as soon as the ongoing type II variation for the reference product Lodoz will be ended.

Additional risk minimisation activities have not been identified for the reference medicinal products. Therefore, a Risk management Plan was not deemed necessary for this product.

**4.3 Pharmacokinetics**

In support of this application a total of four bioequivalence studies were submitted.

The first two studies conducted respectively with the claimed 10 mg/6.25 mg and another non claimed strength (10 mg/25 mg) were not considered conclusive as the analytical technique used in these studies was not adequately validated.

During the CMD referral procedure, two additional and conclusive studies were provided. These studies have investigated respectively the 2.5 mg/6.25 mg and the 10 mg/6.25 mg strengths. In these studies the reference products was the brand leader in France (LODOZ 2.5 mg/6.25 mg and LODOZ 10 mg/6.25 mg from Merck Lipha Santé- France).

In both studies an open label, two-period, two-sequence and two-treatment crossover design was followed. The investigational products were administered as a single-dose after an overnight fast and 21 blood samples were collected up to 48 hours post-dose. A 7 days washout period was observed between the first and the second period.

In each study, 24 healthy volunteers were included. In the study with the lowest strength (2.5 mg/6.25 mg), 22 subjects have completed the study periods and thus were analyzed (two volunteers dropped-out for personal reasons). In the study with the highest strength (10 mg/6.25 mg) 23 subjects have finished all the study periods and thus were analyzed (one volunteer dropped-out for personal reasons).

Plasma concentrations of bisoprolol and HCTZ were monitored in the collected plasma samples by the means of fully validated analytical technique. The primary PK parameters investigated in the study were: AUC0-t, AUC0-inf, Cmax and Tmax.
Table 2.5 mg/6.25 mg: (single-dose under fasting conditions):

**Bisoprolol** Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t\textsubscript{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} hr.ng/ml</th>
<th>AUC\textsubscript{0-∞} hr.ng/ml</th>
<th>C\textsubscript{max} ng/ml</th>
<th>Tmax h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>150.6 (24.6)</td>
<td>156.9 (26.1)</td>
<td>10.56 (1.94)</td>
<td>2.7</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>154 (28.5)</td>
<td>160.7 (29.9)</td>
<td>10.46 (2.08)</td>
<td>2.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>[94;102]%</td>
<td>[94; 102]%</td>
<td>[96;106]%</td>
<td>98.2%</td>
</tr>
<tr>
<td>Point estimate</td>
<td>98%</td>
<td>101.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HCTZ** Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t\textsubscript{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} hr.ng/ml</th>
<th>AUC\textsubscript{0-∞} hr.ng/ml</th>
<th>C\textsubscript{max} ng/ml</th>
<th>Tmax h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>233.5 (43.98)</td>
<td>254 (46.6)</td>
<td>39.07 (9.61)</td>
<td>2.3</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>229.5 (44.5)</td>
<td>250.3 (47.3)</td>
<td>38.41 (5.79)</td>
<td>2.0</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>[97;107]%</td>
<td>[97; 106]%</td>
<td>[92;109]%</td>
<td>102 %</td>
</tr>
<tr>
<td>Point estimate</td>
<td>102 %</td>
<td>100 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10 mg/6.25 mg: (single-dose under fasting conditions):

**Bisoprolol** Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t\textsubscript{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} hr.ng/ml</th>
<th>AUC\textsubscript{0-∞} hr.ng/ml</th>
<th>C\textsubscript{max} ng/ml</th>
<th>Tmax h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>660.2 (117.3)</td>
<td>701.3 (128.2)</td>
<td>43.88 (7.81)</td>
<td>2.0</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>656.8 (109.3)</td>
<td>695.2 (115.6)</td>
<td>44 (7.99)</td>
<td>2.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>[98;103]%</td>
<td>[98; 104]%</td>
<td>[96;104]%</td>
<td>100 %</td>
</tr>
<tr>
<td>Point estimate</td>
<td>100 %</td>
<td>101 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HCTZ** Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t\textsubscript{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t} hr.ng/ml</th>
<th>AUC\textsubscript{0-∞} hr.ng/ml</th>
<th>C\textsubscript{max} ng/ml</th>
<th>Tmax h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>253.4 (81)</td>
<td>277.1 (81.6)</td>
<td>41.1 (11.11)</td>
<td>1.9</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>255 (77.4)</td>
<td>277.5 (77.2)</td>
<td>40.2 (11.9)</td>
<td>2.0</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>[95;103]%</td>
<td>[95; 104]%</td>
<td>[97;109]%</td>
<td>98.8 %</td>
</tr>
<tr>
<td>Point estimate</td>
<td>99.4%</td>
<td>102.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The bioequivalence of the 2.5 mg/6.25 mg and 10 mg/6.25 mg tablets to respective reference products was clearly demonstrated. Waiver from bioequivalence study for the 5 mg/6.25 mg strength was claimed by the applicant and accepted as all the requirements for biowaiver were fulfilled.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Bisoprolol/HCTZ Teva film-coated tablets in the strengths 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg/6.25 mg has been demonstrated. The products are generic forms of the French reference products Lodoz 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10/6.25 mg film coated tablets which are well-known medicinal products with an established favourable efficacy and safety profile.

Satisfactory chemical-pharmaceutical documentation has been provided assuring consistent and sufficient quality of the product.

In support of this application a total of four bioequivalence studies were submitted. Two studies conducted were not considered conclusive as the analytical technique used in these studies was not adequately validated. Moreover, the reference product used in one of the initial two bioequivalence studies was not adequate. The other 2 studies have demonstrated bioequivalence of the 2.5 mg/6.25 mg and 10 mg/6.25 mg tablets to respective reference products demonstrated.

Comments from CMSs have been received and taken into account. Finally, the approved SPC was consistent with that of the presently approved French SPC for Lodoz film coated tablets. However, as a type II variation was ongoing for the reference product Lodoz, the applicant has committed to apply for a type II variation to update both SPC and PIL within 3 months as soon as this ongoing type II variation for the reference product Lodoz will be ended.

The current SPC, Patient Leaflet (PL) and packaging are in the agreed template.