

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Hyporetic 5 mg/12.5 mg, film-coated tablets  
Hyporetic 5 mg/25 mg, film-coated tablets  
Menarini International Operations Luxembourg S.A., Luxembourg  
nebivolol hydrochloride/hydrochlorothiazide**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1068/01-02/DC  
Registration number in the Netherlands: RVG 35174, 35175**

**20 May 2009**

Pharmacotherapeutic group:	beta blocking agents, selective, and thiazides
ATC code:	C07BB
Route of administration:	oral
Therapeutic indication:	treatment of essential hypertension
Prescription status:	prescription only
Date of authorisation in NL:	27 February 2009
Concerned Member States:	Decentralised procedure with AT, BE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NO, PT, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10b fixed combination

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Hyporetic 5 mg/12.5 mg film-coated tablets and Hyporetic 5 mg/25 mg film-coated tablets, from Menarini International Operations Luxembourg S.A.. The date of authorisation was on 27 February 2009 in the Netherlands.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.

The product is indicated for the treatment of essential hypertension.

Hyporetic 5 mg/25 mg fixed dose combination is indicated in patients whose blood pressure is adequately controlled on nebivolol 5 mg and hydrochlorothiazide 25 mg given concurrently.

Hyporetic 5 mg/12.5 mg fixed dose combination is indicated in patients whose blood pressure is adequately controlled on nebivolol 5 mg and hydrochlorothiazide 12.5 mg given concurrently.

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

Hyporetic is a combination of nebivolol, a selective beta-receptor antagonist, and hydrochlorothiazide, a thiazide diuretic. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

This decentralised procedure concerns a so-called fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EU but not hitherto used in combination for therapeutic purposes. In these kinds of applications the results of new pre-clinical tests or new clinical trials relating to that combination have to be provided unless the individual products are often used in combination, which is the case for this combination product. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

Nebivolol was registered by Menarini International Operations Luxembourg in October 1995 in the Netherlands (NL License RVG 18849) for the indication of essential hypertension. In April 1996, the marketing authorisation was extended to other European countries via a MRP. Other names include Nomexor, Nobiten, Nebilox, Temerit and Lobivon 5 mg tablets. A type II variation extending the indication to the treatment of patients with chronic heart failure was completed in 2005. Hydrochlorothiazide has been approved and marketed worldwide for more than 20 years. Hydrochlorothiazide is used in a lot of combinations with other antihypertensive drugs, including beta-blockers.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

##### General information

The active substances are nebivolol hydrochloride and hydrochlorothiazide.

Nebivolol hydrochloride is an established active substance, not described in the USP, the British or European Pharmacopoeias (Ph.Eur.\*). Nebivolol consists of a racemic mixture of two enantiomers: R-

Nebivolol and S-Nebivolol. Both enantiomers are rapidly absorbed following oral administration, regardless of the absence or presence of food. Nebivolol is extensively metabolized, partly to active hydroxy-metabolites. The metabolism of nebivolol via aromatic hydroxylation is highly dependent on CYP2D6 status. Only the aromatic hydroxyl metabolites have comparable pharmacological and binding features as nebivolol. When administered alone only R-nebivolol and not S-nebivolol has blood-pressure lowering activity. However, the antihypertensive action of R-nebivolol is enhanced by the presence of S-nebivolol.

The Active Substance Master File (ASMF) procedure is used for the active substance nebivolol hydrochloride. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Hydrochlorothiazide is an established active substance, described in the USP, the British and European Pharmacopoeias (Ph.Eur.\*). Hydrochlorothiazide is a thiazide diuretic and antihypertensive. It is well absorbed after oral administration and peak plasma concentrations are linearly related to the administered dose. Elimination is primarily by the renal pathway.

The CEP procedure is used for hydrochlorothiazide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

\* *Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

#### Manufacturing process

The manufacturing process of nebivolol hydrochloride, including starting material and reagents, is clearly described in the EDMF.

The manufacturing process of hydrochlorothiazide is covered by the CEP.

#### Quality control of drug substance

The specifications for nebivolol hydrochloride are based on ICH guidelines and batch analysis results.

The specifications for hydrochlorothiazide have been adopted from the CEP and include some additional specifications.

Both sets of specifications are acceptable in view of the various ICH guidelines.

#### Stability of drug substance

Stability data on the active substance nebivolol hydrochloride have been provided for 3 full scale batches stored at 25°C/60% RH (24 months) and 30°/65% RH (24 months) and 40°C/75% RH (6 months). The results show that nebivolol hydrochloride is a chemically and microbiologically stable product. Based on the data submitted, a retest period could be granted of 1 year when stored at or below 25°C.

The active substance hydrochlorothiazide is stable for 5 years. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## Medicinal Product

### Composition

Hyporetic 5 mg/12.5 mg film-coated tablets contain as active substance 5 mg of nebivolol hydrochloride and 12.5 mg hydrochlorothiazide, and are almost pink, round, slightly biconvex film-coated tablets with "5/12.5" embossed on one side and a score line on the other side.

Hyporetic 5 mg/25 mg film-coated tablets contain as active substance 5 mg of nebivolol hydrochloride and 25 mg hydrochlorothiazide, and are almost violet, round, slight biconvex film-coated tablets with "5/25" embossed on one side.

The film-coated tablets are packed in white PP/COC/PP/Alu-blisters.

The excipients are:

#### *Tablet core*

Polysorbate 80 (E433), hypromellose (E464), lactose monohydrate, maize starch, croscarmellose sodium (E468), cellulose microcrystalline (E460), silica colloidal anhydrous (E551), magnesium stearate (E572)

#### *Coating*

Hypromellose (E464), cellulose microcrystalline (E460), macrogol 40 stearate Type I, titanium dioxide (E171), carmines (Carminic acid aluminium lake, E120)

The excipients and packaging are common for this type of dosage form.

The composition of the drug product is based on that of the approved and marketed product Nebivolol 5 mg tablets. Introduction of the second active substance HCTZ was compensated by lowering the amount of lactose monohydrate, keeping the composition and total mass of both tablets constant.

### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The pharmaceutical development is based on the manufacture of the nebivolol tablets. Part of an excipient is replaced by hydrochlorothiazide. The MAH has included dissolution profiles of the original monotherapy tablets which contain nebivolol hydrochloride and tablets containing hydrochlorothiazide. The dissolution profiles show that the dissolution profile of the fixed combination tablet is similar to the original tablets.

### Manufacturing process and quality control of the medicinal product

The tablets are made by wet granulation technique, compression of tablets and film coating. The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

### Excipients

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs or in-house specification when no Ph. Eur. monograph is available.

### Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, diameter, resistance to crushing, average mass, uniformity of dosage units, loss on drying, disintegration time, dissolution, identification, assay, related substances and microbial contamination. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements/limits are not identical. The release and shelf-life specifications/limits are acceptable.

The analytical methods have been adequately described. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 2 pilot scale batches per tablet strength from the proposed production site have been provided, demonstrating compliance with the release specifications. The batch analysis results of full scale batches will be submitted post-approval.

#### Stability tests on the finished product

Stability data on the product have been provided for 3 pilot scale batches stored at 25°C/60% RH (12 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with the ICH stability guideline. The batches were stored in white PP/COC/PP/Aluminium blister.

During the stability testing the following is observed at 25°C, 30°C: a decrease in resistance to crushing, increase in loss on drying and a slight increase in salamide, but these parameters stay well within specifications.

The same is observed in batches stored at 40°C, but the change in salamide content and resistance to crushing is more severe.

Based on the Guideline on Stability testing: Stability testing of existing active substances and related finished products, the proposed shelf life can be extended to twice the period covered by long term stability studies. On the basis of the data submitted, a shelf life was granted of 2 years. No specific storage conditions need to be included in the SPC or on the label.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSA declarations have been submitted and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## **II.2 Non clinical aspects**

Nebivolol hydrochloride and hydrochlorothiazide are well-known active substances often already used in in clinical practice in combination. No new pre-clinical data have been submitted, as the pharmacology, pharmacokinetics and toxicological properties of neбиволol and hydrochlorothiazide are well-known. This is acceptable for this application.

#### **Environmental risk assessment**

The product is intended as a substitute for neбиволol and hydrochlorothiazide products on the market. The approval of this product will not result in an increase in the total quantity of neбиволol or hydrochlorothiazide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## **II.3 Clinical aspects**

#### **Pharmacokinetics**

For this application, the MAH has submitted one study report describing bioequivalence study NEBIZ-01 (P060076).

#### *Design*

The bioequivalence study was designed as a single-dose, crossover study with two patient groups receiving each two treatments during two periods. The wash-out period was at least 13 days. A total of 48 subjects were assigned to 2 groups of 24 subjects (each 12 male and 12 female volunteers). The subjects received the fixed combination tablet containing 5 mg neбиволol and 12.5 mg hydrochlorothiazide in one period and the separate combination of one 5 mg neбиволol tablet and 12.5 mg hydrochlorothiazide during the other treatment period in a randomised design. The other treatment group received the fixed combination tablet containing 5 mg neбиволol and 25 mg hydrochlorothiazide in one period and the separate combination of one 5 mg neбиволol tablet and 25 mg hydrochlorothiazide during the other treatment period. On all occasions the subjects received the assigned medication with 200 ml water after

an overnight fast of 10 hours. Blood samples were performed pre-dose and at 0.5, 0.75, 1, 1.25, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours.

Sixty-seven subjects were screened. A total of 48 healthy male (24) and female (24) Caucasian subjects (aged 18-54 years) entered and completed the study as planned in the protocol, and were available for pharmacokinetic analysis.

### Results

Table 1. Pharmacokinetic parameters for nebivolol (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) after oral administration of 5 mg nebivolol and 12.5 mg HCTZ.

Treatment N= 24	AUC <sub>0-t</sub> ng./ml/h	AUC <sub>0-∞</sub> ng/ml/h	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	26.7 $\pm$ 55.9	31.0 $\pm$ 68.1	3.28 $\pm$ 2.19	1.25 (0.5-4.0)	15.3 $\pm$ 6.0
<b>Reference</b>	29.1 $\pm$ 63.2	35.2 $\pm$ 80.6	3.44 $\pm$ 2.56	1.13 (0.5-5.0)	15.8 $\pm$ 5.2
<b>*Ratio (90% CI)</b>	0.96 (0.89-1.02)	0.94 (0.88-1.01)	1.00 (0.92-1.10)	-	-
<b>CV (%)</b>	19%	20%	27%	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Table 2. Pharmacokinetic parameters for HCTZ (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) after oral administration of 5 mg nebivolol and 12.5 mg HCTZ.

Treatment N= 24	AUC <sub>0-t</sub> ng./ml/h	AUC <sub>0-∞</sub> ng/ml/h	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	472 $\pm$ 169	485 $\pm$ 170	73.0 $\pm$ 29.3	2.0 (1.0-3.0)	9.59 $\pm$ 2.83
<b>Reference</b>	483 $\pm$ 156	494 $\pm$ 158	70.3 $\pm$ 23.4	2.0 (0.75-4.0)	9.21 $\pm$ 1.98
<b>*Ratio (90% CI)</b>	0.97 (0.89-1.04)	0.97 (0.90-1.05)	1.01 (0.92-1.11)	-	-
<b>CV (%)</b>	23%	22%	28%	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Table 3. Pharmacokinetic parameters for nebivolol (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) after oral administration of 5 mg nebivolol and 25 mg HCTZ.

Treatment N= 24	AUC <sub>0-t</sub> ng./ml/h	AUC <sub>0-∞</sub> ng/ml/h	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	17.5 $\pm$ 30.2	21.2 $\pm$ 42.2	2.96 $\pm$ 1.84	1.25 (0.5-4.0)	14.4 $\pm$ 9.24
<b>Reference</b>	19.1 $\pm$ 36.7	22.0 $\pm$ 45.6	2.87 $\pm$ 1.73	1.13 (0.75-5.0)	13.9 $\pm$ 9.48

<b>*Ratio (90% CI)</b>	0.98 (0.91-1.05)	0.97 (0.90-1.05)	1.03 (0.93-1.14)	-	-
<b>CV (%)</b>	21%	23%	29%	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

Table 4. Pharmacokinetic parameters for HCTZ (non-transformed values; arithmetic mean ± SD, t<sub>max</sub> (median, range)) after oral administration of 5 mg nebivolol and 25 mg HCTZ.

<b>Treatment N= 24</b>	<b>AUC<sub>0-t</sub> ng./ml/h</b>	<b>AUC<sub>0-∞</sub> ng/ml/h</b>	<b>C<sub>max</sub> ng/ml</b>	<b>t<sub>max</sub> h</b>	<b>t<sub>1/2</sub> h</b>
<b>Test</b>	1123 ± 326	1142 ± 325	153 ± 41.8	1.5 (1.0-5.0)	10.6 ± 1.9
<b>Reference</b>	1128 ± 351	1145 ± 353	140 ± 40.5	2.5 (1.0-4.0)	11.5 ± 2.9
<b>*Ratio (90% CI)</b>	0.99 (0.94-1.06)	1.00 (0.94-1.06)	1.09 (1.00-1.20)	-	-
<b>CV (%)</b>	18%	18%	27%	-	-
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

### Conclusion and discussion

During the procedure, serious doubts did arise regarding the validity of the used bioanalytical methods, methods for calculation of pharmacokinetic parameters, and statistical methods and outcome. The partial revalidation carried out after completion of the original report to lower the limit of quantitation for hydrochlorothiazide was considered not acceptable. The MAH provided a re-analysis of the plasma samples (see Tables 1-4) with a more sensitive, validated analytical method for the determination of nebivolol and hydrochlorothiazide.

The 90% confidence intervals for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> of nebivolol and HCTZ were in agreement with those calculated by the MAH after re-analyses, and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters, it can be concluded that Hyporetic 5/12.5 mg is bioequivalent to the reference oral formulations 5 mg Nebilet (MAH: Berlin-Chemie, AG) and 12.5 mg hydrochlorothiazide HCT-ISIS (MAH: Alpharma-Isis GmbH & Co). In addition, it can be concluded that Hyporetic 5/25 mg is bioequivalent to the reference oral formulations 5 mg Nebilet and 25 mg hydrochlorothiazide HCT-ISIS (MAH: Novartis Pharma SAS). The choice of the reference product in the bioequivalence study has been satisfactorily justified.

Hyporetic can be taken without reference to food intake; therefore, demonstration of bioequivalence under fasting conditions is in agreement with the CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

No new studies regarding possible pharmacokinetic interactions between nebivolol and hydrochlorothiazide were submitted, since they had already been investigated in a previous study, whose results were described and discussed in the Clinical Overview. In that study, twelve healthy volunteers received 10 mg nebivolol either alone or concomitant with 50 mg hydrochlorothiazide. Main study results include that the C<sub>max</sub> of nebivolol decreased about 20% when concomitantly administered with

hydrochlorothiazide. This study did not indicate a significant interaction of HCTZ on the pharmacokinetics of nebivolol.

### **Pharmacodynamics**

No new data were provided, as the scope of the MAH was to prove essential similarity with an already approved product.

### **Clinical Efficacy**

A multifactorial clinical study comparing the anti-hypertensive effect of different doses of nebivolol (in the range of 1 to 10 mg) and HCTZ (in the range of 12.5 to 25 mg) following 12 weeks of treatment was filed in the original registration dossier of nebivolol for the indication of essential hypertension. As a result the possibility of co-administration of the two medications is already contemplated in the posology section 4.2 of the current nebivolol SPC: *"an additional antihypertensive effect has been observed when Nebilet 5 mg is combined with hydrochlorothiazide 12.5-25 mg"*.

The MAH indicates that the provided documentation is in line with the recommendation of the EMEA document CHMP/EWP/191583/2005, applying to the development of fixed combinations aiming to cover substitution indication with single components that can be administered at the same dose interval and timing and have a wide therapeutic experience and established benefit/risk ratio. An issue during the registration procedure was whether add-on studies are required. Since only a "replacement" indication is requested, and not an add-on indication, and also because the combination is already propagated in the accepted SPC, this was not considered necessary.

### **Clinical Safety**

Nebivolol is widely used in combination with solely hydrochlorothiazide (HCTZ) or in combination with HCTZ and other medication classes in Europe. Information about the co-administration of nebivolol and thiazide diuretics is available from 2 clinical studies conducted in the United States and information on the nebivolol-hydrochlorothiazide combination comes from one clinical phase IV study conducted in Europe. Most frequently reported potential adverse drug reactions were general disorders, nervous system disorders and gastrointestinal disorders: fatigue, dizziness and headache. Information on serious adverse events and deaths from these studies do not raise any special concern. Discontinuation due to adverse events is also not different for combination and monotherapy in these studies.

Information concerning nebivolol comes from PSUR's in the period between 20 April 2000 and 30 April 2005. This safety information focuses on nebivolol monotherapy and it is therefore not possible to differentiate between suspected adverse drug reactions observed under nebivolol monotherapy or those under nebivolol-HCTZ co-administration. The adverse events are in general reflecting the ones mentioned in the SPC. Concerning HCTZ, no post-marketing information has been provided by the MAH. As the nebivolol/hydrochlorothiazide combination is already widely used in clinical practice, and the safety profile of both nebivolol and HCTZ are well known, additional data on use of monotherapy or additional therapy are not needed.

### Risk management plan

As both nebivolol hydrochloride and hydrochlorothiazide are established active substances and are concomitantly used in Europe for the treatment of hypertension, a particular Risk Management Plan is not considered necessary. The MAH will continue to monitor the safety profile of the product, and appropriate actions will be taken as soon as any relevant change to the risk-benefit balance will be identified.

### Pharmacovigilance system

The MAH has a pharmacovigilance system at their disposal. However, at the end of the procedure not all the issues are resolved, and the following deficiency still has to be addressed before the product is placed on the market: The MAH committed to make sure that the procedure on 'Internal audit of the pharmacovigilance system' is in place before the product is placed on the market. The requested information should be submitted within two months after the end of the DCP (20 January 2009).

### **Product information**

#### SPC

The content of the SPC approved during the decentralised procedure is in accordance with those accepted for nebivolol and hydrochlorothiazide products registered in EEA member states.

#### Readability test

The package leaflets of both Hyporetic 5 mg/12.5 mg and Hyporetic 5 mg/25 mg film-coated tablets were prepared on the basis of the text and layout of the package leaflet of Nebivolol 5mg tablets, which had recently been reformatted according to the current QRD template in the English language and successfully tested through a consultation with a group of potential users representative of the target patient group, in accordance with Article 59 and Article 61 of Council Directive 2001/83/EC, as amended by Directive 2004/27/EC.

As important information about the indication and dosage in the PIL of the combination product is different from that reported in the package leaflet of the monotherapy product, the MAH submitted the results of another user test that was carried out focussing on the additional information regarding hydrochlorothiazide in the combination leaflet. Both readability tests are discussed below:

#### *Readability test of the package leaflet of nebivolol 5 mg tablets (Nebilet 5 mg)*

There were three tests, each one with 10 participants. Fourteen questions were asked about the package leaflet. Furthermore, three general questions about the package leaflet were asked. The questions cover the most important parts of the package leaflet.

Taking into account the outcome of first test round the package leaflet and questionnaire has been adapted. The same package leaflet has been used in the second and third round.

The combined results of the second and third rounds of testing demonstrate that the package leaflet has exceeded the minimum score required for evidence of the readability of the package leaflet. Therefore, the package leaflet has not been adapted after the third round.

The package leaflet has been adapted sufficiently taking into account the results of the test.

Attention was paid to the three most important quality aspects: traceability, comprehensibility and applicability. The conclusions are clear and concise and reflect the result of the test.

#### *Readability test of the package leaflet of nebivolol + hydrochlorothiazide (Nebilet Plus)*

A focussed readability test was carried out with six questions referring to the additional information on hydrochlorothiazide. Furthermore, three general questions about the leaflet were asked. The test consisted of three rounds with 10 participants each. In the first round at least 90% of the participants found and answered correctly five questions. For one question this was not the case. The questions have been reworded before the second round. In the second round at least 90% of the 10 participants found and answered correctly all six questions.

In the third round another 10 participants were asked about the question that failed the test in the first round.

There were enough questions about the information of hydrochlorothiazide in the package leaflet. However, there was only one question about section 4 (possible side effects) and this question was very general. The MAH should take this remark into account for further tests. The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Hyporetic 5 mg/12.5 mg film-coated tablets and Hyporetic 5 mg/25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a fixed combination of nebivolol and hydrochlorothiazide. Both nebivolol and hydrochlorothiazide are well-known medicinal products with an established favourable efficacy and safety profile.

#### *Pharmacokinetics*

The separate bioequivalence studies for the 5/12.5 mg and 5/25 mg tablet formulations have been shown in compliance with the requirements of European guidance documents.

A report was submitted and did not indicate a significant interaction of HCTZ on the pharmacokinetics of nebivolol.

#### *Pharmacodynamics*

No new data were provided, as the scope of the MAH was to prove essential similarity to the extemporaneous combination of two already approved products.

#### *Efficacy*

In accordance with the general EMEA guideline CPMP/EWP/238/95, a factorial design study is submitted. Another issue is whether add-on studies are required. Since only a “replacement” indication is requested, and not an add-on indication, and also because the combination is already propagated in the accepted SPC, this is not considered necessary.

#### *Safety*

As the combination is already widely used in clinical practice, and the safety profile of both nebivolol and hydrochlorothiazide are well known, additional data on use of monotherapy or additional therapy are not needed for a better understanding of the safety profile of both substances.

There is one post-approval commitment regarding the Pharmacovigilance System.

The SPC is consistent with that of the reference products. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other nebivolol and hydrochlorothiazide containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hyporetic 5 mg/12.5 mg and Hyporetic 5 mg/25 mg with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 January 2009. Hyporetic 5 mg/12.5 mg film-coated tablets and Hyporetic 5 mg/25 mg film-coated tablets were authorised in the Netherlands on 27 February 2009.

The PSUR submission cycle is 6 months starting from 20 January 2009 for the first two years. Thereafter, 1-yearly PSUR and if necessary a bridging study until 31 March 2012, after which a PSUR will be submitted 3-yearly.

The date for the first renewal will be: 31 November 2012.

The following post-approval commitments have been made during the procedure:

#### Quality - medicinal product

- The MAH committed to provide the validation results of the manufacturing process of three consecutive production scale batches as soon as possible.
- The MAH committed to provide batch analysis data of full-scale batches as soon as possible.

Pharmacovigilance System

- The MAH committed to make sure that the procedure on 'Internal audit of the pharmacovigilance system' is in place before the product is placed on the market. The requested information should be submitted within two months after the end of the DCP.

## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCTZ	Hydrochlorothiazide
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached