PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Jacomox 0.2, 0.3, and 0.4 mg film-coated tablets
Actavis Group PTC ehf, Iceland

moxonidine

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/832/01-03/MR
Registration number in the Netherlands: RVG 33566-8

14 August 2009

Pharmacotherapeutic group: imidazoline receptor agonists
ATC code: C02AC05
Route of administration: oral
Therapeutic indication: mild to moderate essential hypertension
Prescription status: prescription only
Date of first authorisation in NL: 29 March 2006
Concerned Member States: Mutual recognition procedure with CZ, DK, EE, FI, HU, LT, LV, NO, SE, and SK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

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 Jacomox 0.2, 0.3, and 0.4 mg film coated tablets, from Actavis Group PTC ehf. The date of authorisation was on 29 March 2006 in the Netherlands. The product is indicated for mild to moderate essential hypertension.

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

In various animal models it has been shown that moxonidine has a strongly hypotensive effect. Available experimental data indicate that the site of action of moxonidine is located in the central nervous system (CNS). In the brain stem, moxonidine binds selectively to \( \text{I}_1 \)-imidazoline receptors. These imidazoline-sensitive receptors are predominantly found in the rostral ventrolateral medulla, an area which plays an important role in central control of the sympathetic nervous system. The effect of this interaction with these \( \text{I}_1 \)-imidazoline receptors appears to be a reduction in the activity of the sympathetic nerves. This has been demonstrated for cardiac, splanchnic and renal sympathetic nerves.

Moxonidine differs from other centrally acting hypertensives in the fact that it has only a weak affinity for the central \( \alpha_2 \)-adrenergic receptors compared to the affinity for \( \text{I}_1 \)-imidazoline receptors. Alpha\( \alpha_2 \)-adrenergic receptors are considered to be the intermediate pathway that causes sedation and dry mouth, the most commonly observed undesirable effects of centrally acting antihypertensives. Mean systolic and diastolic blood pressure is reduced both at rest and during exercise.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Normatens 0.2, 0.3, and 0.4 mg film coated tablets (NL RVG 15901,15902, and 15903, respectively) which have been registered in the Netherlands by Solvay Pharma B.V. since 1994 (original product). The originator product on the Dutch market has been withdrawn on 31 December 2007, after the mutual recognition procedure was finished (17 October 2006). In addition, reference is made to Normatens authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Cynt 0.2 mg, Physiotens 0.3 mg and Cynt 0.4 mg film-coated tablets, all registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and 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
During the time period of procedure NL/H/0832/01-03/MR the drug substance monoxidine was not described in any pharmacopoeia. Since 01/2005 a Ph.Eur.* monograph on moxonidine is applicable, the current monograph is monograph 01/2008:1758 corrected 6.0. The drug substance is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride and very slightly soluble in acetonitrile. Only one crystalline form is known, produced in most commonly used crystallization solvents. Stereo-isomerism is not applicable.

Manufacture
The Active Substance Master File (ASMF) procedure is used for the active substance. 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/EMEA 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.

Route of synthesis is a two step procedure, in the second step an intermediate is converted to moxonidine. Flow charts for all processing steps are given including all applied quantities of materials and all processing conditions. For all used materials (the starting material, the pre-cursor materials, and all other used reagents and solvents) adequate specifications are applied. Adequate in-process controls are applied at the end of reaction of the moxonidine synthesis.

Specification
During the time period of procedure NL/H/0832/01-03/MR the drug substance specifications of the draft monograph from Pharmeuropa, vol. 12, no. 3, July 2000, have been applied. For impurities the same requirements are applicable as present in the current Ph.Eur. monograph 01/2008:1758 corrected 6.0. In the (draft) monograph 6-chloromoxonidine (EP impurity A) and 4-methoxy-moxonidine (EP impurity B) are the main and specified impurities, and 4-hydroxymoxonidine (EP impurity C) and 6-desmethylmoxonidine (EP impurity D) are listed as potential impurities and limited as any other impurity NMT 0.1%. The drug substance is very pure: all batch results for individual known impurities are below 0.10%, and results for total impurities vary from 0.13-0.21% (requirement: 0.5%). Also other specifications from this draft monograph are applied with additional requirements for heavy metals (NMT 10 ppm), residual solvents (methanol and DMSO with ICH limits) and particle size. Batch analysis results for 6 batches are presented with results meeting the set requirements.

Stability
Three pilot-scale batches have been stored at 25°C/60% RH for 2 years and at 40°C/75% RH for 6 months. The samples are packed in double LDPE bags, put in a sealed aluminium bag, which is put in a mini fibre drum, mimicking the commercial packaging. Test parameters are description, loss on drying, HPLC related substances and HPLC assay. The drug substance appears to be very stable: all assay results are $\geq 99.0\%$, and all total impurities results are in the range 0.18-0.28%. Herewith the claimed re-test period of 5 years without specific storage condition is justified.

* 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.
Medicinal Product

Composition
The drug product is a film-coated tablet comprising 0.2-0.3-0.4 mg monoxidine. The three compositions are almost the same; differences in active strength are compensated by adaptation of the quantity lactose monohydrate, and the differences in colourant content are compensated by adaptation of the film-coat quantity.
The tablets are packed in Alu-PVC/PVdC blister packaging. The packaging is usual for this type of dosage form.

The excipients are:
Tablet core: lactose monohydrate, crospovidone, povidone K25, and magnesium stearate.
Film-coating: hypromellose, titanium dioxide (E171), macrogol 400, and red iron oxide (E172).
All applied excipients are well-known and safe in the proposed concentrations.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the application product is qualitatively similar to the composition of the innovator reference product. Comparative analyses on impurities showed that the main impurities for the proposed product and the innovator product are identical, and that the observed levels in the proposed product are acceptable. It confirms that the chosen excipients are indeed compatible.
Comparative dissolution studies with the innovator product (Physiotens 0.4 mg) and originator products from other CMSs were satisfactory, and the dissolution profiles were almost identical. In all batches of the proposed product, including the test bio-batch, the applied particle size specification for the drug substance (NLT 80% < 20 µm, NLT 96% < 50 µm) appears to be appropriate and adequate.
The use of the German reference products is acceptable.

Excipients
The colourant iron oxide, red complies with the monograph of USP-NF. According to the certificate of analysis from the supplier the colourant is also meeting the requirements of colourants in food (E 172).
For the coating excipient Opadry Y-1-7000 it is stated that its components hypromellose, titanium dioxide and Macrogol 400 comply with the concerning Ph.Eur. monographs. Specifications for the composed Opadry product are considered adequate. All other excipients comply with Ph.Eur. requirements. In conclusion the specifications for the excipients are acceptable.

Manufacturing process
A flow-chart of the manufacturing process is present with indication of the in-process controls. The process comprises the usual steps of wet granulation, lubrication, compression and coating. Due to the low active contents the active substance is first diluted with lactose monohydrate for obtaining a better homogeneity. Concise descriptions are given. The MAH provided data on essential parameters of the manufacturing process, for instance mixing times and mixing speeds, sieve sizes, drying times, moisture contents after drying, for the various stages in the manufacturing process.
There are two manufacturers of the finished product. The given batch formulae are based on batches from these manufacturers. The maximum batch size from both manufacturers has been based on validation of 3 batches each. The manufacturing formulae are in accordance with the product formulae for each strength.

Product specification
The product specification includes tests appearance, HPLC and UV identification of moxonidine, average weight and uniformity of mass, KF water content, disintegration, dissolution (NLT 85% at 20 min), hardness, HPLC assay and uniformity of dosage units (Ph.Eur. 2.9.40), HPLC related substances, and microbiological purity. Based on the stability data, the shelf-life requirements are widened for assay and related substances. The analytical methods have been adequately described and validated.
Batch analysis results for full-scale batches from both manufacturers are present for all strengths. All results meet the set release specifications.
Stability tests on the finished product
The claimed shelf life is 24 months in PVC/PVdC-Alu blister packaging when stored not above 30°C. Test parameters are appearance, average tablet weight, hardness, disintegration, dissolution, water content, assay and related substances. 10 batches from one manufacturer (4 of the 0.2 mg strengths, and 3 each of the other strengths) have been stored at 25°C/60% RH for 24 months, at 30°C/60% RH for 12 months, and at 40°C/75% RH for 6 months. 5 batches from another manufacturer (2 batches of the 0.2 and 0.4 mg strengths, and one batch of the 0.3 mg strength) have been stored at 25°C/60% RH for 24 months, and at 30°C/60% RH for 12 months. The results justify the claimed shelf-life of 24 months if stored not above 30°C in the proposed packaging.

The MAH committed that three commercial scale batches from one manufacturer will be put on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Regarding Lactose monohydrate the supplier stated that the milk is sourced from healthy animals in the same condition as milk collected for human consumption. Herewith the excipient is excluded from the scope of the NiG on Minimising the risk on TSE.
Regarding Magnesium stearate the supplier stated that the excipient is from vegetable origin. There are no other substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects
This product is a generic formulation of Normatens, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
This product is intended to substitute for other identical products on the market. The approval of this product does not result in an increase of the total quantity of moxonidine released into the environment. It does not contain any component which result in additional hazard to the environment during storage, distribution, use and disposal.
II.3 Clinical aspects

Moxonidine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted 3 bioequivalence studies in which the pharmacokinetic profile of the test products Jacomox 0.2, 0.3, and 0.4 mg tablets were compared with the pharmacokinetic profiles of the German reference products Cynt 0.2, Physiotens 0.3 mg and Cynt 0.4 mg tablets, respectively.

The choice of the reference product in the bioequivalence studies have been justified by comparison of dissolution results and compositions of reference products in different member states (AT, DE, DK, FR and UK).

The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Moxonidine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of moxonidine. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

**Bioequivalence study 1 – 0.4 mg under fasted conditions**

*Reference:* Cynt 0.4 mg tablets (Lilly, Germany)  
*Test:* Jacomox 0.4 mg tablets (Actavis Group PTC ehf, Iceland)

A single-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 13 healthy, non-smoking male volunteers aged 18 to 27 years. Each subject received a single dose (0.4 mg) of one of the 2 moxonidine formulations. The tablet was orally administered with 240 ml water after an overnight fast. Standardized food was only allowed 5, 10, and 23.5 hours after drug-intake. There were two dosing periods, separated by a washout period of 7 days. Blood samples were collected over a period of 24 hours (16 samples). All thirteen subjects were eligible for pharmacokinetic analysis. The method of measuring plasma moxonidine is well described and a validation report has been submitted. The statistical evaluation was assessed and shown to be correct.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=13</th>
<th><strong>AUC</strong>&lt;sub&gt;0-24h&lt;/sub&gt; ng.h/ml</th>
<th><strong>AUC</strong>&lt;sub&gt;0-∞&lt;/sub&gt; ng.h/ml</th>
<th><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
<th><strong>t</strong>&lt;sub&gt;max&lt;/sub&gt; h</th>
<th><strong>t</strong>&lt;sub&gt;1/2&lt;/sub&gt; h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td></td>
<td>9.01 ± 1.05</td>
<td>9.11 ± 1.08</td>
<td>3.45 ± 0.70</td>
<td>0.5 (0.5 – 1.0)</td>
<td>2.15 ± 0.14</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td></td>
<td>9.32 ± 1.33</td>
<td>9.42 ± 1.35</td>
<td>3.66 ± 0.60</td>
<td>0.5 (0.5 – 1.0)</td>
<td>2.12 ± 0.13</td>
</tr>
<tr>
<td><strong>Ratio (90% CI)</strong></td>
<td>---</td>
<td>0.97 (0.93 – 1.01)</td>
<td>0.94 (0.83 – 1.06)</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td></td>
<td>---</td>
<td>6.4</td>
<td>17.2</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

| **AUC**<sub>0-24h</sub> | area under the plasma concentration-time curve from time zero to 24 hours.  
| **AUC**<sub>0-∞</sub> | area under the plasma concentration-time curve from time zero to infinity.  
| **C**<sub>max</sub> | maximum plasma concentration.  
| **t**<sub>max</sub> | time for maximum concentration.  
| **t**<sub>1/2</sub> | half-life.  

*In-transformed values
The 90% confidence intervals calculated for AUC₀₋₄, AUC₀₋∞ and Cₘₐₓ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of moxonidine under fasted conditions, it can be concluded that Jacomox 0.4 mg tablets and Cynt 0.4 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Bioequivalence study 2 – 0.2 mg under fasted conditions**

*Reference:* Cynt 0.2 mg tablets (Lilly, Germany)
*Test:* Jacomox 0.2 mg tablets (Actavis Group PTC ehf, Iceland)

A single-dose, randomised, crossover bioequivalence study was carried out under fasted conditions in 20 healthy, male volunteers aged 18 to 36 years. Each subject received a single dose (0.2 mg) of one of the 2 moxonidine formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period. For each subject there were 2 dosing periods, separated by a washout period of 7 days. A randomisation scheme was included in the report. Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 14 hours after administration of the products. One subject withdrew for personal reasons. Nineteen subjects were therefore eligible for pharmacokinetic analysis. The method of measuring plasma moxonidine is well described and a validation report has been submitted. The statistical evaluation was assessed and shown to be correct.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=19</th>
<th>AUC₀₋₄ pg.h/ml</th>
<th>AUC₀₋∞ pg.h/ml</th>
<th>Cₘₐₓ pg/ml</th>
<th>tₘₐₓ h</th>
<th>t₁/₂ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4738 ± 756</td>
<td>4883 ± 755</td>
<td>1993 ± 472</td>
<td>0.50 (0.50 – 1.33)</td>
<td>2.2 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>4809 ± 892</td>
<td>4951 ± 901</td>
<td>1854 ± 411</td>
<td>0.75 (0.50 – 1.67)</td>
<td>2.3 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>---</td>
<td>0.99 (0.95 – 1.02)</td>
<td>1.07 (0.98 – 1.16)</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>---</td>
<td>6.0</td>
<td>14.3</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

AUC₀₋₄ is area under the plasma concentration-time curve from zero to t hours
AUC₀₋∞ is area under the plasma concentration-time curve from zero to infinity
Cₘₐₓ is maximum plasma concentration
tₘₐₓ is time for maximum concentration
t₁/₂ is half-life

*In-transformed values

The 90% confidence intervals calculated for AUC₀₋₄, AUC₀₋∞ and Cₘₐₓ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of moxonidine under fasted conditions, it can be concluded that Jacomox 0.2 mg tablets and Cynt 0.2 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Bioequivalence study 3 – 0.3 mg under fasted conditions**

*Reference:* Physiotens 0.3 mg tablets (Solvay, Germany)
*Test:* Jacomox 0.3 mg tablets (Actavis Group PTC ehf, Iceland)

A single-dose, randomised, crossover bioequivalence study was carried out under fasted conditions in 20 healthy, male volunteers aged 18 to 54 years. Each subject received a single dose (0.3 mg) of one of the 2 moxonidine formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period. For each subject there were 2 dosing periods, separated by a washout period of 7 days. A
randomisation scheme was included in the report. Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 14 hours after administration of the products. All twenty subjects were eligible for pharmacokinetic analysis. The method of measuring plasma moxonidine is well described and a validation report has been submitted. The statistical evaluation was assessed and shown to be correct.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of moxonidine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=20</th>
<th>AUC\text{0-t} (pg.h/ml)</th>
<th>AUC\text{0-∞} (pg.h/ml)</th>
<th>C\text{max} (pg/ml)</th>
<th>t\text{max} (h)</th>
<th>t\text{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>6503 ± 772</td>
<td>6660 ± 747</td>
<td>2633 ± 448</td>
<td>0.75 (0.50 – 1.00)</td>
<td>2.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>6426 ± 805</td>
<td>6593 ± 792</td>
<td>2448 ± 425</td>
<td>0.75 (0.50 – 1.33)</td>
<td>2.3 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90%CI)</td>
<td>---</td>
<td>1.01 (0.98 – 1.04)</td>
<td>1.08 (1.01 – 1.15)</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>---</td>
<td>5.5</td>
<td>12.1</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitions</th>
<th></th>
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<tbody>
<tr>
<td>AUC\text{0-t}</td>
<td>area under the plasma concentration-time curve from time zero to t hours</td>
</tr>
<tr>
<td>AUC\text{0-∞}</td>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
<tr>
<td>C\text{max}</td>
<td>maximum plasma concentration</td>
</tr>
<tr>
<td>t\text{max}</td>
<td>time for maximum concentration</td>
</tr>
<tr>
<td>t\text{1/2}</td>
<td>half-life</td>
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</table>

*ln-transformed values

The 90% confidence intervals calculated for AUC\text{0-t}, AUC\text{0-∞} and C\text{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of moxonidine under fasted conditions, it can be concluded that Jacomox 0.3 mg tablets and Physiotens 0.3 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**
Moxonidine was first approved in 1991, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of moxonidine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.
Product information

SPC
SPC is in accordance with the SPCs of moxonidine products already harmonised in the EU by other MRPs, for example NL/H/397; 398; 406/01-03.

Readability test
A readability test has been performed. The test was diagnostic, which is acceptable. The test consisted of two different parts, one to test the usability and the other to test the readability of the PIL.
First a pre-test was performed with 3 participants for quality assurance to optimize the test questionnaire. The aim of the pre-test was to ensure the comprehensiveness of the specific questionnaire for the PIL to be tested and to check the interview length. The main test was performed with 22 participants. This test did not lead to any changes in the Patient Information Leaflet. It did however lead to three recommendations:

- Reduce the information as the PIL was considered to elaborate
- Emphasize the presence of lactose as ingredient
- Date of expiration should be easier to locate, as 50% of the participants were not able to locate this information

The results have been translated into sufficient recommendations relating to text passages and particular aspects of the text. The patient information leaflet has not been adapted taking into account the results of the test. The first recommendation of the readability test has not led to an adaptation in the PIL because the length of the PIL could not be shortened as all the information has to be included in the PIL. The second and the third recommendation could not have led to an adaptation in the PIL because the PIL has to follow the QRD template.

The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Jacomox 0.2, 0.3, and 0.4 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Normatens tablets. Normatens is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

SPC is in accordance with the SPCs of Moxonidine products already harmonised in the EU by other MRPs, for example NL/H/397; 398; 406/01-03.

The Board followed the advice of the assessors. Jacomox was authorised in the Netherlands on 29 March 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Jacomox with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 17 October 2006.

The first PSUR will cover the period from October 2006 to October 2009. The second PSUR will cover a 2-year period to coincide with the renewal. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 17 October 2011.

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

Quality – medicinal product

- The MAH committed to put three batches of commercial batch size from one drug product manufacturer on stability according to the approved stability program.
List of abbreviations

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