PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Diltiazem HCl retard CF 200 mg and 300 mg,
prolonged-release capsules, hard
Centrafarm B.V., the Netherlands
diltiazem hydrochloride

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/2691/001-002/DC
Registration number in the Netherlands: RVG 112064, 112066

31 July 2013

Pharmacotherapeutic group: selective calcium channel blockers with direct cardiac effects, benzothiazepine derivatives
ATC code: C08DB01
Route of administration: oral
Therapeutic indication: stable angina pectoris; mild to moderate hypertension
Prescription status: prescription only
Date of authorisation in NL: 21 June 2013
Concerned Member States: Decentralised procedure with BE, ES, LU
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 Diltiazem HCl retard CF 200 mg and 300 mg, prolonged-release capsules, hard from Centrafarm B.V. The date of authorisation was on 21 June 2013 in the Netherlands.

The product is indicated for stable angina pectoris and mild to moderate hypertension.

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

Diltiazem inhibits the transport of calcium ions by the slow channels during depolarisation of the cell membrane. This effect occurs on myocardial cells and smooth muscle tissue of the coronary and peripheral arteries. As a result, diltiazem increases flow in the coronary arteries and decreases peripheral arterial resistance. This mechanism contributes to increasing the oxygen supply to the myocardium. Diltiazem widens the vessels and improves arterial compliance. This vessel widening in hypertensive patients leads to a decrease in blood pressure due to reduced peripheral resistance, without causing reflex tachycardia. However, a mild decrease in heart rate has been observed. Irrigation of the internal organs and in particular the kidneys as well as coronary circulation are preserved or increased.

A mild sodium-lowering effect has been observed after acute administration. During long-term treatment with diltiazem, there is no stimulation of the renin-angiotensin-aldosterone system (RAAS). Diltiazem also causes no water and salt retention as shown by the lack of change in body weight and plasma water and electrolyte balance. Proteinuria is also reduced during treatment of hypertension with diltiazem.

Diltiazem reduces left ventricular cardiac hypertrophy in patients with hypertension. It has little effect on cardiac output. Diltiazem has a slight negative inotropic effect and is contraindicated in sick sinus syndrome. It decreases atrioventricular conduction. Diltiazem has no effect on conduction in the bundle of His.

Diltiazem has no effect on the regulation of blood sugar levels and lipid metabolism.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Tildiem XR 200 mg and 300 mg prolonged-release capsules, hard (NL License RVG 16538-16539) which have been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 3 October 1994 (original product). The first marketing authorisation was granted for MonoTildiem LP 300 mg prolonged-release capsules, registered by Sanofi-Aventis since 1992 in France. In addition, reference is made to Tildiem 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 product MonoTildiem LP 300 mg capsules registered in France, under fasting, fed and steady-state conditions. 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. This 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.
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 this product type 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
The active substance is diltiazem hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, crystalline powder, which is freely soluble in water, methanol and methylene chloride, and slightly soluble in anhydrous ethanol. The active substance shows optical rotation.

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/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.

Manufacturing process
Diltiazem hydrochloride is manufactured in a three step process. Ethanol is used in the last step of the synthesis. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents, particle size distribution and microbiological quality. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 11 full scaled batches stored at 25°C/65% RH (24-60 months) and 3 full scaled batches stored at 40°C/75% RH (6 months). Based on the results, the proposed retest period of 60 months without any special storage requirements was granted.

*Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Diltiazem HCl retard CF 200 mg has an opaque white capsule cap and body and contains a combination of white to off-white pellets (granules).
Diltiazem HCl retard CF 300 mg has an opaque green capsule cap and an opaque white capsule body and contains a combination of white to off-white pellets (granules).
The hard capsules are packed in PVC/PVDC/aluminium blister packs.

The excipients are:
- Capsule content - povidone K30, ethyl cellulose (E462), talc, stearic acid
- Capsule-shell 200 mg - titanium dioxide (E171), gelatin
- Capsule-shell 300 mg - titanium dioxide (E171), gelatin, Quinoline yellow (E104), Indigotine (E132)

The two different capsule strengths are fully dose proportional with regard to their capsule content.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed concerned the optimization of the composition and manufacturing process of the coated pellets to optimize the dissolution properties. The choices of the packaging and manufacturing process are justified. The 300 mg test batch used in the bioequivalence study was manufactured according to the finalized process and formulation. Comparative dissolution testing versus the innovator product showed similarity. The pharmaceutical development of the product has been adequately performed. The biowaiver for the 200 mg strength was supported by relevant comparative dissolution data.

Manufacturing process
The manufacturing process can be subdivided into three main steps: the preparation of active uncoated pellets, preparation of the coated pellets and filling into capsules of the desired size and content. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches and one full-scale batch per strength of drug product. The preparation of the active uncoated pellets was validated on three full-scale batches and the preparation of the active coated pellets was validated on two full-scale and two pilot-scale batches.

Control of excipients
The excipients comply with the requirements of the Ph.Eur. Quinoline yellow and indigotine comply with Directive 2008/128/EC.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, average weight, uniformity of dosage units, uniformity of weight, related substances, dissolution, residual solvents and microbiological quality. The release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and have in general been adequately validated. The stability indicating nature of the method for related substances has been demonstrated. Batch analytical data from the proposed production site have been provided on one full-scale and two pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on one full-scale and two pilot-scale batches per strength stored at 25°C/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PVDC/Al-blisters. Except for an increase of one impurity no trends or changes were seen. All tested parameters remained well within the acceptable limits. The MAH demonstrated that diltiazem in solid state is stable at daylight exposure. Moreover, the film-coated pellets are protected from light by the capsule shells. The product does not need to be stored in the original package to protect from light. Based on the results of stability testing, the proposed shelf-life of 36 months and storage condition ‘Store below 30°C’ were granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for the gelatin used in the manufacture of the capsules, no substances of ruminant origin are present in the product nor have any been used in the manufacturing of the product. For gelatin Certificates of suitability issued by the EDQM have been provided.
II.2 Non-clinical aspects

This product is a generic formulation of Tildiem XR, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of diltiazem 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

Diltiazem is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Diltiazem HCl retard CF 300 (Centrafarm B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product MonoTildiem LP 300 mg capsules (Sanofi-aventis, France). The MAH carried out single-dose studies under fasted and fed conditions (Study I and II), and one multiple-dose study was under fasted conditions as required for modified-release formulations according European guideline (NfG CPMP/EWP/QWP 1401/98).

The choice of the reference product

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study I – single-dose, fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy subjects (17 males, 13 females), aged 18-50 years. Each subject received a single dose (300 mg) of one of the 2 diltiazem formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 19, 20, 22, 24, 30, 36 and 48 hours after administration of the products.

The study design is acceptable. The sampling period is long enough and the sampling frequency is high enough. Blood plasma samples were used to determine the parent compound diltiazem, but also the metabolites desacetyldiltiazem and N-desmethyldiltiazem. The assessment was based on the parent compound only, in compliance with the Guideline on the investigation of bioequivalence.

Results
During the wash-out of the first period, 1 female subject withdrew for personal reasons. A total of 29 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of diltiazem under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=29</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-\infty}</th>
<th>C_{max}</th>
<th>t_{max}</th>
<th>t_{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>2627 ± 897</td>
<td>2704 ± 944</td>
<td>140 ± 42</td>
<td>9 (6-12)</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>2560 ± 805</td>
<td>2637 ± 847</td>
<td>138 ± 40</td>
<td>9 (16-14)</td>
<td>--</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.02 (0.97-1.08)</td>
<td>1.02 (0.97-1.08)</td>
<td>1.02 (0.96-1.09)</td>
<td>--</td>
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</tr>
</tbody>
</table>

*ln-transformed values

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-\infty} and C_{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 diltiazem under fasted conditions, it can be concluded that Diltiazem HCl retard CF 300 mg and MonoTildiem LP 300 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Study II – single-dose, fed conditions**

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy subjects (16 males, 14 females), aged 18-51 years. Each subject received a single dose (300 mg) of one of the 2 diltiazem formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 19, 20, 22, 24, 30, 36 and 48 hours after administration of the products.

The study design is acceptable. The sampling period is long enough and the sampling frequency is high enough. Only the data on the parent compound diltiazem have been assessed.

*Results*

Before dosing of the second period 1 female subject was withdrawn due to vomiting. Therefore there are a total of 29 subjects completing the study and included in the pharmacokinetic and statistical analyses.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of diltiazem under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=29</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-\infty}</th>
<th>C_{max}</th>
<th>t_{max}</th>
<th>t_{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>3239 ± 1283</td>
<td>3300 ± 1315</td>
<td>250 ± 86</td>
<td>6 (5-9)</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>3277 ± 1233</td>
<td>3340 ± 1260</td>
<td>252 ± 87</td>
<td>6 (5-14)</td>
<td>--</td>
</tr>
</tbody>
</table>
The 90% confidence intervals calculated for $AUC_0-t$, $AUC_0-\infty$ and $C_{max}$ 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 diltiazem under fed conditions, it can be concluded that Diltiazem HCl retard CF 300 mg and MonoTildiem LP 300 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Study III – multiple-dose, fasted conditions**

*Design*

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy subjects (19 males, 11 females), aged 18-54 years. The two treatment periods each start with a run-in period of 3 days and a clinic day of 24 hours. Single doses diltiazem 300 mg prolonged release capsules were taken 24-hourly at day -3, -2, -1 and the clinic day. Blood samples were drawn pre-dose and at 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 19, 20, 22 and 24 hours post dose. There was a wash-out of 8 days between periods.

The study design is acceptable. The sampling period is long enough and the sampling frequency is high enough. As in the single-dose studies, only the data on the parent compound were assessed.

*Results*

Before dosing of the second period 1 male subject was withdrawn due to influenza. Therefore there are a total of 29 subjects completing the study and included in the pharmacokinetic and statistical analyses.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_\tau$</th>
<th>$C_{max,ss}$</th>
<th>$C_{min,ss}$</th>
<th>$T_{max,ss}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=29</td>
<td>ng/ml/h</td>
<td>ng/ml</td>
<td>ng/ml</td>
<td>h</td>
</tr>
<tr>
<td>Test</td>
<td>3084 ± 1311</td>
<td>193 ± 83</td>
<td>66 ± 25</td>
<td>7 (2-14)</td>
</tr>
<tr>
<td>Reference</td>
<td>2964 ± 881</td>
<td>193 ± 57</td>
<td>65 ± 27</td>
<td>7 (2-11)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) 1.03 (0.91-1.16) 0.98 (0.88-1.10) 1.05 (0.87-1.25)

The 90% confidence intervals calculated for $AUC_\tau$, $C_{max,ss}$ and $C_{min,ss}$ 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 diltiazem at steady state, it can be concluded that Diltiazem HCl retard CF 300 mg and MonoTildiem LP 300 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
Safety
In the fasted study, a total of 12 adverse events were reported: around the intake of the reference product: 6 subjects reported headache. Around intake of the test product: headache (3), nausea (1), Elevated AST (1) and dizziness (1).
In the fed study, a total of 32 adverse events were reported: around the intake of the reference product: 13 subjects reported headache, 1 nausea. Around intake of the test product: headache (14), nausea (1), vasovagal attack (1), flushing (1), and palpitations (1).
In the multiple-dose study, a total of 51 adverse events were reported. Around the intake of the reference product: headache (19), Epistaxis (1) and heart palpitations (1). Around the intake of the test product: headache (17), hot flushes (1), nausea (4), migraine (1), epistaxis (2), flushing of ears (2), flushing (1), palpitations (1) and chest discomfort (1).

Biowaiver
A biowaiver for the 200 mg capsule is claimed. The following conditions should be fulfilled:
- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional.
- the dissolution profiles should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Pharmacokinetics are linear over the dosage range and the different strengths are manufactured by the same manufacturing process. The qualitative and quantitative composition of the different strengths is similar. Although there are differences in composition of the cap of the capsule, the main ingredients are dose proportional. This is a multiple unit formulation; the different strengths are different capsules with both the same pellets of the active substance. A biowaiver can be granted for the 200 mg strength.

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
Diltiazem was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of diltiazem can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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
In general, the proposed SPC is consistent with currently approved in the Dutch SPC of the originator Tildiem XR and the Core Safety Profile (CSP) for diltiazem as agreed during the PSUR worksharing procedure DK/H/PSUR/0017/001.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. Inclusion and exclusion criteria were well described. The studied population consisted of a demographic group of adults (12 females and 8 males) with an emphasis on the elderly (15 subjects over 45 years of age) and those with lower levels of education. The interviewed population is acceptable.
The test was performed by face-to-face interviews. The developed questionnaire contained 13 questions specific to the content of the PIL and 3 questions specific to evaluate readability, comprehensibility and lay-out, design and structure of the PIL.

A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. The data showed that all questions met the passing criteria in the first and second round. Based on the user test, an acceptable adjustment was made to the description of the adverse event frequency categories in section 4.

There were sufficient questions about the critical sections, and the areas concerning traceability, comprehensibility and applicability were sufficiently covered. The results of the test were satisfactory. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Diltiazem HCl retard CF 200 mg and 300 mg, prolonged-release capsules, hard have a proven chemical-
pharmaceutical quality and are generic forms of Tildiem XR 200 mg and 300 mg capsules. Tildiem XR 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 for modified-release formulations under fasted and fed conditions, and at steady state.

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

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the
agreed templates.

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 Tildiem XR 200 mg and 300 mg with the reference product, and have therefore
granted a marketing authorisation. The decentralised procedure was finished on 8 May 2013. Tildiem XR
200 mg and 300 mg prolonged-release capsules, hard were authorised in the Netherlands on 21 June
2013.

The date for the first renewal will be: 8 May 2018.

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

Quality - medicinal product
- The MAH committed to continue the on-going stability studies for the drug product until 36 months of
  long-term storage.
- The MAH committed to include the first three production scale batches per strength of drug product in
  the stability program according to the stability protocol.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<tr>
<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</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>
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<td>Scope</td>
<td>Procedure number</td>
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