CBG MEB

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

## Citalopram CF 30 mg and 60 mg, film-coated tablets Centrafarm Services B.V., the Netherlands

## citalopram hydrobromide

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/310/004-005/MR**
**Registration number in the Netherlands: RVG 31114, 31115**

**2 September 2010**

| | |
|---|---|
| Pharmacotherapeutic group: | antidepressants, selective serotonin reuptake inhibitors |
| ATC code: | N06AB04 |
| Route of administration: | oral |
| Therapeutic indication: | major depressive episodes |
| Prescription status: | prescription only |
| Date of first authorisation in NL: | 23 September 2005 |
| Concerned Member States: | Mutual recognition procedure with DE |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(3) |

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 Citalopram CF 30 mg and 60 mg, film-coated tablets, from Centrafarm Services B.V. The date of authorisation was on 23 September 2005 in the Netherlands. The product is indicated for treatment of major depressive episodes.

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

Citalopram is a bi-cyclic isobenzophurane-derivative that is chemically not related to tricyclic and tetracyclic antidepressants or other available antidepressants. The main metabolites of citalopram are also selective serotonin uptake inhibitors, though to a lesser degree. The metabolites are not reported to contribute to the overall antidepressant effect.
The antidepressant effect is probably connected with the specific inhibition of serotonin uptake in the brain neurons. Tolerance to this inhibitory effect does not occur during long-term treatment. Citalopram has almost no effect on the neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid. Citalopram shows no affinity, or only very little, for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.

This mutual recognition procedure concerns a line extension; for three other strengths, i.e. 10 mg, 20 mg and 40 mg film-coated tablets, an MRP was positively finalised on 20 December 2001 (NL/H/310/001-003/MR). In the Netherlands, the Marketing Authorisation for the 30 and 60 mg strengths was based on art 10(3) of EEC-Directive 2001/83/EC - hybrid application, since these strengths have never been registered for the Dutch innovator product Cipramil. Reference is made to the Danish innovator product Cipramil as the reference medicinal product authorised in the EEA for at least 6/10 years. In the Netherlands, Cipramil 20 mg and 40 mg coated tablets (NL License RVG 19593 and 19594) have been registered by Lundbeck B.V since 16 April 1997. The difference in strength is deemed acceptable, because the new strengths are in agreement with the posology. In addition, reference is made to Cipramil authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) 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 provided the results obtained in two bioequivalence studies performed previously with the 20 mg and 40 mg Citalopram CF tablets. These products were compared to innovator products from the French and German market, respectively. It was demonstrated that the results can be extrapolated to the 30 and 60 mg strengths. 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 hybrid products can be used instead of their reference products.

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, as this is not required for a hybrid 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 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**
The active substance is citalopram hydrobromide, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*). It is a white to almost white, odourless, crystalline powder. It is sparingly soluble in water and acetone, and soluble in methanol. The substance is a racemate. The clinical activity of citalopram is believed to reside in the S-enantiomer of citalopram whereas the R-enantiomer is inactive. Polymorphism is not exhibited by this substance. Particle size is controlled but this aspect is not critical for quality.

The Active Substance Master File (ASMF) procedure is used for both suppliers of 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
The manufacturing processes of the drug substance manufacturers are documented sufficiently detailed in the DMF, including all critical control quality aspects. Acceptable specifications have been adopted for the starting material, solvents and reagent used.

Quality control of drug substance
The drug substance specification of the MAH for quality control has been established by an in-house monograph, based on the manufacturing processes. The specification contains adequate limits, including limits for assay and for residuals of impurities, based on the solvents and other materials used in these processes and formed by-products. In general, it covers the individual specifications appropriately.
The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for a total of 8 production batches from both sources.

Stability of drug substance
For the substance from the two sources, two different retest periods for the substance have been issued: two years with no special storage conditions for one source, and four years, *do not store above 25°C,* for the other supplier. These retest periods are adequate in view of the stability data submitted. Sufficient production batches have been included, with a study design according to ICH.

** 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
Citalopram CF 30 mg contains as active substance 37.485 mg citalopramhydrobromide, equivalent to 30 mg citalopram, and is a round, white tablet with a break-line and diameter of 9 mm.
Citalopram CF 30 mg contains as active substance 74.97 mg citalopramhydrobromide, equivalent to 60 mg citalopram, and is an oval, white tablet with a break-line and diameter of 8,5 x 16 mm.

Both tablets can be divided into equal halves.

The 30 and 60 mg tablets are dose proportional and are also dose proportional with the 20 and 40 mg formulations used in the bioequivalence study. The dissolution profiles of the proposed tablet doses of 30 mg and 60 mg are also in accordance with the 20 mg and 40 mg dose used in the BE studies and fall within the specification.

The film-coated tablets are packed in packed in PVC/PVDC/Al blisters, 100x1 unit dose blisters and HDPE tablet containers with a LDPE tamper evident cap.

The excipients are:
*Core* - mannitol, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate
*Coating* - hypromellose, macrogol 6000, titanium dioxide (E171).

Pharmaceutical development
The tablets are white, film-coated tablets with different dimensions and a scoring line. The development of these strengths has been satisfactorily performed and explained. The development studies submitted are partially based on the previously authorised 10, 20 and 40 mg tablet strengths (NL/H/310/001-003/MR). The excipients are well known substances and are usual for immediate release film-coated tablets. Functionality of the scoring line has been demonstrated with results complying to Ph. Eur. uniformity tests for the halved tablets. Bioequivalence between the tablets and the innovators has been demonstrated. Two tablet strengths were used: 20 (French innovator) and 40 mg (German innovator). Comparative dissolution profiles further support this equivalence.
Suitability of the release dissolution method has been demonstrated and the dissolution is rapid; the results of the development batches as well as the production batches are in accordance with the set limit. Particles size does not influence the dissolution. The containers have been demonstrated to be suitable for storage of the tablets and are safe.
The pharmaceutical development has been adequately described.

Manufacturing process
The manufacturing process is a standard process and consists basically of a dry-mixing method for the cores. Content uniformity during the mixing steps has been demonstrated. Process validation has been performed on production scale batches.

Control of excipients
The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The drug product specifications for release and at end-of-shelf-life comprise all parameters to assess quality of solid dosage forms, and include appearance, average and uniformity of dosage units, disintegration, dissolution, microbiological purity, assay and impurities. Limits are acceptable, including impurities, which comply with the guideline for impurities in new drug products. Batch analysis data of several production batches of both strengths have been submitted from the approved sites, with results according to specifications.

Stability of drug product
Stability data have been provided on three production-scale batches of each strength stored at 25°C/60% RH (36 months) and 40°C/75%RH (6 months). Both containers were studied. No significant change was observed for any parameter at any measuring point.
Based on the results, a shelf-life of 3 years is considered appropriate for the product in both containers. The study design was according to ICH criteria. No special storage condition is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no 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. The magnesium stearate used is of vegetable origin.

## II.2 Non clinical aspects

This active substance has been available on the European market for over 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

**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 citalopram 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

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

Two bioequivalence studies have been submitted in support of the current application. In the first study Citalopram CF 40 mg is compared with Cipramil 40 mg (Lundbeck, Germany). A second study was performed in view of a change in the active substance supplier; in this study, the Citalopram CF 20 mg tablet is compared with Seropram 20 mg (Lundbeck, France).

*The choice of the reference products*
The choice of the reference products in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

Bioequivalence study I
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 20 healthy male subjects, aged 24-45 years. Each subject received a single dose (40 mg) of one of the 2 citalopram formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of at least 21 days.
Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12, 16, 24, 36, 48, 72, 96, and 120 hours after administration of the products.

*Analytical/statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
There were no drop-outs. All 20 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of citalopram under fasted conditions.

| **Treatment N=20** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 1378 ± 366 | 1572 ± 461 | 35 ± 8 | 4.00 (1.00 - 7.00) | 39 ± 5 |
| **Reference** | 1395 ± 346 | 1615 ± 511 | 36 ± 7 | 4.00 (1.50 -7.00) | 41 ± 9 |
| ***Ratio (90%** | - | 0.98 | 0.98 | - | - |

| | | | | | |
|---|---|---|---|---|---|
| **CI)** | | (0.94 - 1.01) | (0.94 - 1.03) | | |
| **CV (%)** | - | 7.0 | 8.0 | - | - |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of desmethyl-citalopram under fasted conditions.

| **Treatment N=20** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 351 ± 56 | 602 ± 143 | 4.1 ± 0.6 | 36.0 (9.00 - 36.1) | 87 ± 33 |
| **Reference** | 361 ± 56 | 592 ± 128 | 4.1 ± 0.8 | 36.0 (1.5 - 72.2) | 80 ± 25 |
| ***Ratio (90% CI)** | - | 0.99[1] (0.93 - 1.06) | 0.99[2] (0.96 - 1.03) | - | - |
| **CV (%)** | - | 11.3[1] | 6.62[2] | - | - |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
[1] not statistically significant; n=17
[2] not statistically significant; n=19
**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-\infty}$ 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 citalopram under fasted conditions, supported by metabolite data, it can be concluded that Citalopram CF 40 mg and Cipramil 40 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.

Bioequivalence study II

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 21 healthy male subjects, aged 24-45 years. Each subject received a single dose (20 mg) of one of the 2 citalopram formulations. The tablet was orally administered with 200 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours after administration of the products.

*Analytical/statistical methods*

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

*Results*

Three subjects dropped out from the study: one for personal reasons, one due to protocol violation and one because of vomiting after administration of the study medication. The remaining 18 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of citalopram under fasted conditions.

| **Treatment N=18** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 660 ± 129 | 717 ± 153 | 16 ± 3 | 3.5 (1.5 - 7.0) | 46 ± 13 |
| **Reference** | 709 ± 149 | 764 ± 171 | 17 ± 3 | 3.75 (1.5 - 9.0) | 43 ± 10 |
| ***Ratio (90% CI)** | 0.93 (0.90 - 0.96) | 0.94 (0.91 - 0.97) | 0.95 (0.89 - 1.01) | - | - |
| **CV (%)** | 4.9 | 5.5 | 10.6 | - | - |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of desmethyl-citalopram under fasted conditions.

| **Treatment N=18** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 220 ± 38 | 321 ± 93 | 2.2 ± 0.4 | 35 (2 - 47) | 89 ± 38 |
| **Reference** | 237 ± 43 | 338 ± 93 | 2.3 ± 0.4 | 35 (2.5 - 72) | 87 ± 37 |
| ***Ratio (90% CI)** | 0.93 (0.86 - 1.00) | 0.95 (0.88 - 1.08) | 0.97 (0.93 - 1.01) | - | - |
| **CV (%)** | 11.8 | 10.8 | 6.3 | - | - |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

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 citalopram under fasted conditions, supported by metabolite data, it can be concluded that Citalopram CF 20 mg and Seropram 20 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.

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

*Extrapolation to 30 mg and 60 mg strengths*
The 30 mg and 60 mg tablets are dose proportional with the 20 and 40 mg test products used in the bioequivalence studies. Since the tablets are manufactured by the same manufacturers and process, dissolution profiles are comparable, and citalopram exhibits linear pharmacokinetics, the results obtained in the bioequivalence studies can be extrapolated to the 30 mg and 60 mg tablets.

The MEB has been assured that the bioequivalence study has 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
Citalopram was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of citalopram 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
The SPC is in line with the SPC of other citalopram containing products recognized through MRP. Concomitant use with pimozide has been included as a contraindication in accordance with the product information of the NL originator product, as well as the current SPC for NL/H/310/001-003. In addition, the January 2008 PhVWP core wording on suicide/suicidal thoughts and clinical worsening has been implemented. The SPC was harmonised with the SPC currently approved for NL/H/0310/001-003.

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 was diagnostic and scoring. This is acceptable because several questions on relevant items were posed to test the readability of the PIL so that at least 80% of the test persons could find and understand the information properly. Twenty persons participated in the test, which was conducted as a single round test. A total of 15 questions were asked; the nature of the questions was such that both the aspects of comprehensibility and usability of the PIL were tested.
All answers were put into one of 18 categories ranging from *finding the information very easily and interpreting the information correctly* to *finding the information with lots of difficulties despite being given some assistance and interpreting the information erroneously* and *failing to give a correct answer because the message was not understood or the information was not found*.
All individual scores (categories) were presented. All questions except for one met the pre-set criteria for passing the test. The section that failed to pass the test concerned concomitant use of MAOIs. An alternative, simplified text was proposed. However, as stated in the QRD-template, complex details should not be omitted from the leaflet, and on request of the RMS a general statement to ask the doctor for advice was added instead of deleting information from the leaflet. A second advice for amendment given in the report concerns the interaction with St. John's wort. Although this is not required as the question passed the test, this advice has been taken into account, which is agreed upon by the RMS. The test itself and the test report are of sufficient quality.

The tested leaflet is not identical to the leaflet currently approved. As compared to the tested leaflet in German, some information has been added in accordance with the SPC, a few amendments were made

in accordance with the current QRD-template, and amongst others the January 2008 PhVWP core wording has been implemented. Although the changes are of such nature that the test results are considered applicable to the current leaflet, the MAH committed to perform a new user test on this PIL.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Citalopram CF 30 mg and 60 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are approvable hybrid forms of Cipramil 20 mg and 40 mg coated tablets. Cipramil is a well-known medicinal product with an established favourable efficacy and safety profile. The difference in strength is deemed acceptable, because the new strengths are in agreement with the posology.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The results of bioequivalence studies performed with Citalopram CF 20 mg and 40 mg tablets have been shown to be applicable to the 30 and 60 mg strengths as well.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other citalopram containing products.

The Board followed the advice of the assessors. Citalopram CF 30 mg and 60 mg, film-coated tablets were authorised in the Netherlands on 23 September 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Citalopram CF 30 mg and 60 mg with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 8 July 2008.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from July 2008 to July 2011.

The date for the first renewal will be: 8 July 2013.

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

Product information
- The MAH committed to perform a readability test on the newly established PIL.

## List of abbreviations

| | |
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| 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 |
| $C_{max}$ | 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 |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MAIO | Monoamine Oxidase Inhibitor |
| 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 |
| $t_{½}$ | Half-life |
| $t_{max}$ | 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 |
|---|---|---|---|---|---|---|
| Optimization of the scoring line of the medicinal product. | NL/H/0310/ 004/II/032 | II | 13-3-2009 | 12-5-2009 | Approval | N |