PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Topiramaat Torrent 25/50/100/200/400 film-coated tablets
Torrent Pharma GmbH, Germany

topiramate

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/1667/001-005/DC
Registration number in the Netherlands: RVG 104609,104611-104614

10 August 2010

Pharmacotherapeutic group: Antiepileptics
ATC code: N03AX11
Route of administration: oral
Therapeutic indication: adults, adolescents and children aged over 6 years: partial seizures with or without secondary generalised seizures, and generalised tonic-clonic seizures (monotherapy); children aged 2 years and above, adolescents and adults: partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures, seizures associated with Lennox-Gastaut syndrome (adjunctive therapy); adults: prophylaxis of migraine headache after careful evaluation of possible alternative treatment options

Prescription status: prescription only
Date of authorisation in NL: 20 May 2010
Concerned Member States: Decentralised procedure with DE, IT, LT, PL, and RO
Application type/legal basis: Directive 2001/83/EC, Article 10(1) and 10(3) (only 400 mg strength)

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 Topiramaat Torrent 25, 50, 100, 200, and 400 film-coated tablets, from Torrent Pharma GmbH. The date of authorisation was on 20 May 2010 in the Netherlands. The product is indicated:

- as monotherapy in adults, adolescents and children aged over 6 years of age with partial seizures with or without secondary generalised seizures, and generalised tonic-clonic seizures.
- as adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
- as prophylaxis for migraine headache in adults after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

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

Topiramate is an antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainite/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of topiramate antiepileptic activity.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Topamax 25 mg, 50 mg, 100 mg and 200 mg tablets (NL license RVG 24165-24168) which have been registered in Poland since 1999 by Janssen-Cilag B.V. (original product). In addition, reference is made to Topamax authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. Only for the 400 mg tablets, the marketing authorization is granted based on article 10(3) (hybrid application).

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Topamax 200 mg tablets, 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. 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.

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 generic medicinal products.
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 topiramate, a known active substance. Topiramate is not described in the European Pharmacopoeia (Ph.Eur.*), but is described in the USP. The active substance is slightly soluble in water and freely soluble in acetone, chloroform, dimethylsulphoxide, ethanol and methylene chloride. Topiramate does not exhibit polymorphism.

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.

Manufacture
Topiramate is synthesized in a two-step synthesis. No class 1 solvents or heavy metal catalysts have been used in the manufacturing process. The active substance has been adequately characterized. The starting materials, reagents and solvents are controlled adequately.

The MAH has committed to perform process validation on full production scale batch sizes post-approval, using three batches of each strength. The validation data or report will be made available at plant and the same can be provided on request.

Quality control of drug substance
The drug substance specification is established in-house by the MAH. The specification is acceptable in view of the route of synthesis, the USP monograph on topiramate and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three-full scaled batches stored at refrigerated (2-8°C; 24 months), long-term (25°C/60%RH; 24 months) and accelerated (30°C/65%RH; 12 months) storage conditions. The batches were adequately stored.

After 12 months of accelerated storage, the description was out of specification. Under long-term conditions and refrigerated conditions high variability of most parameters was observed, but all results remain within limits. The claimed retest period of 24 months is deemed justified when stored below 25°C. The photostability of the drug substance has been demonstrated.

The MAH has committed to continue stability studies of up to 60 months as per protocol (as provided) and final approved specification of drug substance.

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

Composition

Five strengths are developed containing 25 mg, 50 mg, 100 mg, 200 mg and 400 mg topiramate, respectively.

Topiramaat Torrent 25 are white to off white, round, biconvex, film-coated tablets debossed ‘1031’ on one side and ‘25’ on the other side.

Topiramaat Torrent 50 are yellow coloured, round, biconvex, film-coated tablets, debossed with breakline on both sides, separating ‘10’ & ‘32’ on one side and ‘50’ on the other side. The tablet can be divided into two equal halves.

Topiramaat Torrent 100 are white to off white coloured, round, biconvex with bevelled edge, film-coated tablets with cross break lines on the both sides. The tablet can be divided into four equal quarters.

Topiramaat Torrent 200 are peach coloured, round, biconvex, film coated, tablets debossed with breakline on both sides, separating ‘10’ & ‘34’ on one side and ‘200’ on the other side. The tablet can be divided into two equal halves.

Topiramaat Torrent 400 are white to off white coloured, round, biconvex with bevelled edge, film-coated tablets with cross break lines on the both sides. The tablet can be divided into four equal quarters.

The different strengths are dose proportional with respect to the core tablet. The composition and amount of the film-coating is only dose proportional between the 100mg and 400mg strengths.

The excipients are:

**Tablet core:** lactose monohydrate, microcrystalline cellulose (E460), pregelatinized maize starch, sodium starch glycolate Type A, silica, colloidal anhydrous, talc (E553b), and magnesium stearate (E572).

**Tablet coating:** hypromellose 2910 (E464) (6 cps), macrogol 400, titanium dioxide (E171), ferric oxide yellow (E172) (only 50 mg and 200 mg), ferric oxide red (E172) (only 200 mg).

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

The film-coated tablets are packed in blister packs containing cold form blister foil and plain aluminium foil (OPA/Aluminium/PVC/Aluminium).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified as they are all well-known and their functions stated. Dissolution testing has been performed with Ph.Eur. type II apparatus (paddle) at 50 rpm and 900 mL medium, in water, acetate buffer, and phosphate buffer. More than 90% was dissolved in 15 minutes in all cases, demonstrating essential similarity. The development of the manufacturing process was adequately described and the choice of packaging material and microbiological attributes are justified. The bio-batch has been manufactured by the same manufacturing process and site as the other batches. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by dry mixing of sifted topiramate, lactose monohydrate and microcrystalline cellulose, addition of the binder solution (pregelatinised starch in purified water), drying and sifting of the granules, blending with sifted colloidal anhydrous silica and sodium starch glycolate, lubrication with sifted magnesium stearate and talc, compression, coating and packing. Process validation data on the product has been presented for 12 production scaled batches. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full production scaled batches will be performed post authorisation, using three batches of each strength.

Excipients

The excipients comply with the EP (European Pharmacopoeia) or the USP-NF (U.S. Pharmacopoeia–National Formulary) (iron oxides). These specifications are acceptable.
Quality control of drug product
The product specification includes tests for description, identification (HPLC, IR and colourants), average weight, water content, disintegration time, dissolution, uniformity of dosage units, assay, related substances, microbiological control and uniformity of weight of subdivided tablets. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 12 production scaled batches, demonstrating compliance with the release specification.

Breakability:
Results of subdivision of tablets have been provided for halves of the uncoated and coated tablets of the 50 mg and 200 mg strengths and for quarters of the uncoated and halves of the coated tablets of the 100 mg and 400 mg strengths. All results are well within the 85-115% range and the uniformity of mass of the subdivided tablets has been demonstrated adequately. Although the coated tablets of the 100 mg and 400 mg strengths are divided into halves only, the results are all between 96% and 104% of the average mass and no significant differences are expected after coating for the quarter tablets. The provided breakability data is deemed sufficient.

Stability tests on the finished product
Stability data on the product has been provided 12 production scaled batches stored at long-term (25°C/60%RH; up to 24 months), intermediate (30°C/65%RH; 12 months) and accelerated (40°C/75%RH; 6 months) storage conditions. The conditions used in the stability studies are according to the ICH stability guideline. The batches were adequately stored.
Under accelerated stability conditions, out of specification results were found for the 200 mg and 400 mg tablets for sulfate and description respectively. Therefore, intermediate stability studies were performed on these strengths. The intermediate storage conditions demonstrated a decrease in assay.
The 24 months of long-term stability data demonstrate a slight decrease in assay as well. For the other parameters no clear trends could be observed. All results remain within limits.
The bulk pack of the 25 mg, 50 mg and 100 mg tablets was tested under accelerated conditions for 6 months, demonstrating a decrease in assay, an increase in water content and a decrease in bacterial count respectively. The 200 mg and 400 mg tablets were tested for 6 months under long-term storage conditions as OOS results for sulfate and description were found under accelerated conditions. No clear trends could be observed. A photostability study has been performed on one batch of each strength. The results demonstrate photostability of the drug product. The claimed shelf-life of 24 months can be granted and the acceptable storage conditions are “no specific storage conditions” for the 25, 50 and 100mg strengths and “Do not store above 30°C” for the 200 and 400mg tablets.
The MAH has committed to continue the stability studies up to 60 months and to place the third production scaled batch of each strength on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate, for which a TSE statement has been provided, 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.

II.2 Non clinical aspects
This product is a generic formulation of Topamax, 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
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 topiramate 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Topiramaat Torrent 200 mg film-coated tablets (Torrent Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Topamax 200 mg tablets (Janssen-Cilag GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

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

Study design
A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study was carried out under fasted conditions in 26 healthy adult male volunteers, aged 19-32 years. Each subject received a single dose (200 mg) of one of the 2 topiramate formulations. The tablet was orally administered with 200 ml water after overnight fasting for at least 10 hours. A lunch was served 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected within one hour before dosing and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 144.0 and 192.0 hours after administration of the products.

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

Topiramate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of topiramate. 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.

Results
There were 46 adverse events in the study of which 42 were considered to be related to the study formulations. 21 adverse events were observed with the test formulation and 21 adverse events were observed with the reference formulation. There were a significant number of dropouts (11) in the second period that did not complete the study. These subjects did not tolerate the study drugs favourably in the first period. All adverse events were mild in intensity and resolved completely without any sequelae, except for 1 subject (Pharyngitis) who could not be contacted for follow-up. There were no serious adverse events in the trial.

Fourteen subjects completed both treatment periods. One subject was withdrawn due to positive test on THC. All subjects were analysed but only the 14 who completed both periods were statistical evaluated.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of topiramate under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ), µg.h/ml</th>
<th>( \text{AUC}_{0-\infty} ), µg.h/ml</th>
<th>( C_{\text{max}} ), µg/ml</th>
<th>( t_{\text{max}} ), h</th>
<th>( t_{1/2} ), h</th>
</tr>
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<tbody>
<tr>
<td>Test</td>
<td>174 ± 32.5</td>
<td>180 ± 34.1</td>
<td>4.55 ± 0.83</td>
<td>1.5 (0.67 – 4.5)</td>
<td>40.6 ± 6.9</td>
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<tr>
<td>Reference</td>
<td>173 ± 28.0</td>
<td>179 ± 29.6</td>
<td>4.55 ± 0.77</td>
<td>1.8 (0.33 – 5.5)</td>
<td>40.7 ± 7.9</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.98 – 1.03)</td>
<td>1.00 (0.97 – 1.03)</td>
<td>1.00 (0.95 – 1.06)</td>
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<tr>
<td>CV (%)</td>
<td>3.8%</td>
<td>4.1%</td>
<td>8.0%</td>
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</table>

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( C_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration
\( t_{1/2} \) half-life

*ln-transformed values

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) 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 topiramate under fasted conditions, it can be concluded that Topiramaat Torrent 200 mg film-coated tablets and Topamax 200 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.

Extrapolation of results to other strengths
All conditions for a bio waiver to the other strengths have been met. Therefore, the results of the bioequivalence study performed with the 200 mg film-coated tablets therefore apply to the other strengths.

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
The MAH submitted a Risk Management Plan. No important identified risks, no important potential risks and no important missing information are present.

The MAH reports that Routine Pharmacovigilance Practices includes

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner
- The preparation of reports for regulatory authorities:
- Expedited adverse drug reaction (ADR) reports
- Periodic Safety Update Reports (PSURs)
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities
- Other requirements, as defined by local regulations.

Concerning a Risk Minimisation Plan the MAH states that considering the above evaluations and based on the fact that no safety concern with the innovator product has been identified a risk minimisation plan is not considered as necessary.
Product information

SPC
At the time of writing this PAR, an Art. 30 referral was ongoing on harmonization of the Innovator’s SPC of Topamax. Paediatric labelling is expected to be included in the SPC as a result of this Referral.

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.
One pilot test (n=2) and two test rounds (per round n=10) were performed with 22 participants in total. Participants were recruited by placing an advertisement in a local newspaper. However, no information was provided upon the medication of the participants, neither the experience with the disease. In total there were 22 questions (4 general questions, 15 questions about finding / comprehensibility / applicability and 3 final questions which provide overall feedback). This is considered acceptable.
In both rounds all participants were able to find the correct information and all participants were able to answer the questions correctly (a satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PIL, and 90% of all participants can show that they understand and can act upon it).
Since the results of this test indicate that the PIL is well structured and organised, easy to understand and written in a comprehensible manner, the package leaflet can be qualified as acceptable.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Topiramaat Torrent 25/50/100/200/400 film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Topamax 200 mg tablets. Topamax 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.

The SPC, package leaflet and labelling are in the agreed templates. The MAH committed to adapt these texts according to the outcome of the ongoing Art. 30 referral. Braille conditions are met by the MAH.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Topiramaat Torrent 25/50/100/200/400 film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 April 2010. Topiramaat Torrent 25/50/100/200/400 film-coated tablets are authorised in the Netherlands on 3 May 2010.

Considering the well-established use of this generic the proposed PSUR submission schedule (3-yearly) can be endorsed. Topiramate takes part in the EU Harmonised Birth Dates project of the Heads of Medicines Agencies. The first PSUR should be submitted with a data lock point of January 2012.

The date for the first renewal will be: 12 April 2015.

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

**Quality - active substance**
- The MAH has committed to continue stability studies of up to 60 months as per protocol (as provided) and final approved specification of drug substance.

**Quality – medicinal product**
- The MAH has committed to continue the stability studies up to 60 months and to place the third production scaled batch of each strength on stability.
- The MAH has committed to perform process validation on full production scale batch sizes post-approval, using three batches of each strength. The validation data or report will be made available at plant and the same can be provided on request.
- The MAH committed to adapt the SPC and labelling texts according to the outcome of the ongoing Art. 30 referral.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<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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<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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<tr>
<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>$C_{\text{max}}$</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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<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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<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>
</tr>
<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>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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