

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

**Ibuprofen (als lysine) Mylan OTC 200 mg
and 400 mg, film-coated tablets
Mylan B.V., the Netherlands**

ibuprofen (as lysine)

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/2550/001-002/DC
Registration number in the Netherlands: RVG 111362-111363**

26 November 2013

Pharmacotherapeutic group:	anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivative
ATC code:	M01A E01
Route of administration:	oral
Therapeutic indication:	mild to moderate pain (see next page)
Prescription status:	non prescription
Date of authorisation in NL:	9 September 2013
Concerned Member States:	Decentralised procedure with BE, IE, IT, LU, PL; DE (400 mg only)
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 Ibuprofen (als lysine) Mylan OTC 200 mg and 400 mg, film-coated tablets from Mylan B.V. The date of authorisation was on 9 September 2013 in the Netherlands.

The 200 mg product is indicated for:

- symptomatic treatment of mild to moderate pain, such as headache, dental pain, period pain and fever and pain in the common cold.

The 400 mg product is indicated for:

- symptomatic treatment of mild to moderate pain, such as headache, acute migraine headache with or without aura, dental pain, period pain and fever and pain in the common cold.

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

Ibuprofen lysine is the lysine salt of ibuprofen, a propionic acid derivative. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory-related pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

Ibuprofen (R/S) comprises half as the S(+) enantiomer which is pharmacologically active as a prostaglandin (PG) synthesis inhibitor and the other half mass as R(-) ibuprofen which is less active as a PG synthesis inhibitor but which may have some pharmacological properties relevant to the anti-inflammatory actions of ibuprofen.

Following oral administration, ibuprofen lysine dissociates to ibuprofen acid and lysine. Lysine has no recognised pharmacological activity. The pharmacological properties of ibuprofen lysine, therefore, are the same as those of ibuprofen acid.

This decentralised procedure concerns a hybrid application with reference to the innovator product NurofenFlash, which was first registered in the Europe in 2000. This product, containing 200 mg or 400 mg ibuprofen as ibuprofen lysine, is also registered under different names, such as Nurofen Express TAB (PL) and Nurofen Omhulde tabletten (NL). In a number of member states, EU reference products are used because the innovator product is not available in one of the strengths.

The marketing authorisation is granted based on article 10(3), of Directive 2001/83/EC, hybrid application with limited indications compared to the innovator product.

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 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 two bioequivalence studies in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products NurofenFlash® 200 mg and 400 mg tablets from the French market. 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 hybrid 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 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 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 ibuprofen (as lysine), an established active substance which does not have an official monograph in the European Pharmacopoeia (Ph.Eur.*). The active substance is freely soluble in water. Ibuprofen D,L-lysine is a racemic mixture of ibuprofen (as lysine) salt, obtained using a racemic 50% aqueous solution of D,L-lysine and ibuprofen. There is no evidence of polymorphism for ibuprofen (as lysine).

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

The active substance is synthesized using the starting materials ibuprofen and D,L-lysine. The suppliers of the ibuprofen starting material are all granted a CEP. For D,L-lysine, the synthetic route is laid down and an adequate specification is given.

Quality control of drug substance

The drug substance specification has been established in-house and is in line with the ASMF specification except for the particle size specification. 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 one full-scale batch. Furthermore, the active substance manufacturer has provided the results of three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided by the active substance manufacturer for 10 full-scale batches stored at 25°C/60% RH (60 months) and 3 full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) No changes or trends can be observed and all parameters are within specification. Based on the stability results, a re-test period of 5 years (no storage conditions) is justified.

* *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

Ibuprofen (als lysine) Mylan OTC 200 mg is a white to off-white, film-coated, round, biconvex, bevelled edge tablet imprinted with "M" over "IL1" in black ink on one side of the tablet and blank on the other side. Ibuprofen (als lysine) Mylan OTC 400 mg is a white to off-white, film-coated, oval biconvex, bevelled edge tablet imprinted with "M IL2" in black ink on one side of the tablet and blank on the other side.

The tablets are packed in blisters composed of PVC/Aclar or OPA/Al/PVC and HDPE bottles.

The excipients are:

Core - microcrystalline cellulose (E460), colloidal anhydrous silica (E551), croscopvidone (E1202), povidone (E1201), magnesium stearate (E572), talc (E553b).

Tablet coating - polyvinyl alcohol hydrolysed (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b)

Printing ink - shellac (E904), iron oxide black (E172), ammonium hydroxide (E527).

The two strengths are dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batches used is identical to the marketed product. A biowaiver for the lower product strength was considered not acceptable, since ibuprofen as a weak acid displays limited solubility in acidic environment which leads to differences in dissolution between strengths at lower pH, *i.e.* 1.2 and 4.5. This observation was reported for both test and reference products, confirming that dissolution differences are due to the active substance rather than due to formulation effect. During the DCP, the results of an additional bioequivalence study for the lower product strength have been provided.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by wet granulated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The core excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. These specifications are acceptable. The coating and the ink are controlled by in-house specifications.

Quality control of drug product

The product specification includes tests appearance, identity, assay, degradation, loss of drying, dissolution, uniformity of dosage units and microbiological purity.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the products have been provided 3 pilot-scale batches of each tablet strength stored at 25°C/60% RH (18 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 the intended blisters and HDPE container.

Under long-term and accelerated conditions the batch results remain within specification. Photostability studies showed that the product is not sensitive to light. A 2 year shelf-life, with no specific storage conditions, is acceptable in view of the provided stability data.

Satisfactory in-use stability data covering 60 days are provided, hence an in-use shelf life of 60 days is accepted for the 48's and 100's count HDPE bottles. The 200's tablet packs are meant as dispensing packs.

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. Magnesium

stearate is derived from material of vegetable origin and stearic acid used as a raw material is produced from natural palm oil.

II.2 Non-clinical aspects

This product is a hybrid formulation of NurofenFlash, 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 ibuprofen lysine 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

Ibuprofen 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.

As lysine has no recognised pharmacological activity, the pharmacological properties of ibuprofen lysine are the same as those of ibuprofen acid.

For this hybrid application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Ibuprofen (als lysine) Mylan OTC 200 mg and 400 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product NurofenFlash® 200 mg and 400 mg tablets (Reckitt Benckiser Healthcare International Limited, UK). The study with the lower strength was conducted because ibuprofen as a weak acid displays limited solubility in acidic environment which explained that comparative dissolution of the 200 mg and 400 mg products could not be demonstrated at the lower pH values.

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.

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.

Bioequivalence study I – 200 mg, fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 18-45 years. Each subject received a single dose (200 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 240 ml water after an overnight fast of approximately 10 hours. Subjects remained fasting for at least 4 hours after administration. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00 and 12.00 hours after administration of the products.

The study design is acceptable, and the washout period is considered adequate ($t_{1/2}$, 1-2 hours).

Results

Thirty-four subjects completed both periods of the study and were included in pharmacokinetic and statistical analysis. Two subjects did not report to the facility in period 2, hence withdrawn from the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of R-ibuprofen under fasted conditions.

Treatment N=34	AUC ₀₋₁₂ µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	23.734 \pm 7.3485	26.588 \pm 7.2099	11.462 \pm 2.4730	0.50 (0.33 - 2.00)	1.4 \pm 0.20
Reference	25.464 \pm 8.1580	28.505 \pm 8.2016	12.939 \pm 3.1578	0.50 (0.33 - 1.50)	1.48 \pm 0.29
*Ratio (90% CI)	0.94 (0.87 – 1.02)	0.94 (0.88 – 1.01)	0.90 (0.83 – 0.97)	--	--
CV (%)	19.6	17.9	19.1	--	--
AUC_{0-∞} 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					

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of S-ibuprofen under fasted conditions.

Treatment N=34	AUC ₀₋₁₂ µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	33.327 \pm 11.2469	37.610 \pm 12.5891	11.546 \pm 2.0043	0.50 (0.33 - 2.00)	2.10 \pm 0.47
Reference	33.039 \pm 11.8016	37.305 \pm 13.1474	12.416 \pm 2.4323	0.50 (0.17 - 1.75)	2.12 \pm 0.54
*Ratio (90% CI)	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.03)	0.94 (0.88 – 0.99)	--	--
CV (%)	5.7	4.9	15.0	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC₀₋₁₂, AUC_{0-∞} 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 R-ibuprofen and S-ibuprofen under fasted conditions, it can be concluded that Ibuprofen (als lysine) Mylan OTC 200 mg and NurofenFlash® 200 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.

Safety

The oral administration of test and reference products was generally well tolerated. One subject had an adverse event after administration of the reference product and one subject had a serious adverse event, also after administration of reference product. Both adverse events were registered in the post-study safety assessment. Both adverse events were judged to be possibly related to the study treatment. The second subject had increased creatinin and urea in the post study safety assessment. The adverse event was considered serious by the Principal Investigator and required hospitalization. The medical condition of the subject was managed with pharmacotherapy and followed up till normalization.

Bioequivalence study II – 400 mg, fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-38 years. Each subject received a single dose (400 mg) of one of the 2 ibuprofen formulations. The tablet was orally administered with 240 ml water after an overnight fast of approximately 10 hours. Subjects remained fasting for at least 4 hours after administration. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00 and 12.00 hours after administration of the products.

The study design is acceptable, and the washout period is considered adequate ($t_{1/2}$, 1-2 hours).

Results

Two subjects did not report to the facility in period 2, and were therefore withdrawn from study. In total, 34 subjects completed both periods. A total of 34 subjects were included in the principle pharmacokinetic and statistical analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of R-ibuprofen under fasted conditions.

Treatment N=34	AUC ₀₋₁₂ µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	50.7 \pm 11.0	53.4 \pm 11.0	20.7 \pm 3.03	0.50 (0.33 – 1.25)	1.23 \pm 0.23
Reference	50.9 \pm 12.1	53.9 \pm 12.1	22.5 \pm 5.35	0.67 (0.33 – 1.50)	1.31 \pm 0.28
*Ratio (90% CI)	1.00 (0.95 – 1.05)	0.99 (0.95 – 1.04)	0.93 (0.88 – 0.98)	--	--
CV (%)	12.4	11.8	13.2	--	--

AUC_{0-∞} 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

**In-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of S-ibuprofen under fasted conditions.

Treatment N=34	AUC ₀₋₁₂ µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
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Test	67.2 ± 21.1	71.7 ± 21.4	20.8 ± 3.76	0.67 (0.33 – 1.50)	2.20 ± 0.43
Reference	64.7 ± 21.3	69.2 ± 21.5	22.1 ± 4.81	0.67 (0.33 – 1.50)	2.20 ± 0.43
*Ratio (90% CI)	1.04 (1.01 – 1.08)	1.04 (1.02 – 1.07)	0.95 (0.91 – 0.99)	--	--
CV (%)	7.21	6.22	10.2	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC₀₋₁₂, AUC_{0-∞} 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 R-ibuprofen and S-ibuprofen under fasted conditions, it can be concluded that Ibuprofen (als lysine) Mylan OTC 400 mg and NurofenFlash® 400 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.

Safety

No deaths or serious adverse events were reported during this study. Only one adverse event of mild nausea was reported from one subject during the entire duration of the study. It was considered possibly related to administration of test product, and was resolved after an hour.

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

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

Ibuprofen was first approved in 1969, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ibuprofen 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

The content of the SPC approved during the decentralised procedure is generally in accordance with that accepted for the reference product NurofenFlash, with a difference in indications.

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 2 participants,

followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both test rounds 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibuprofen (als lysine) Mylan OTC 200 mg and 400 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are hybrid forms of NurofenFlash 200 mg and 400 film-coated tablets. NurofenFlash 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 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 Ibuprofen (als lysine) Mylan OTC 200 mg and 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 July 2013. Ibuprofen (als lysine) Mylan OTC 200 mg and 400 mg, film-coated tablets were authorised in the Netherlands on 9 September 2013.

The date for the first renewal will be: 23 July 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{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
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 _{1/2}	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