CBG MEB

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

# Simvastatine Accord 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets Accord Healthcare Ltd, United Kingdom

# simvastatin

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/1314/001-004/MR**
**Registration number in the Netherlands: RVG 100363-100366**

**10 May 2010**

| | |
|---|---|
| Pharmacotherapeutic group: | HMG CoA reductase inhibitors |
| ATC code: | C10AA01 |
| Route of administration: | oral |
| Therapeutic indication: | treatment of hypercholesterolaemia or mixed dyslipidaemia, and reduction of cardiovascular mortality and morbidity in risk patients |
| Prescription status: | prescription only |
| Date of first authorisation in NL: | 22 November 2007 |
| Concerned Member States: | Mutual recognition procedure with BE, BG, CZ, DE, EE, FR, LT, LV, PL, PT, RO, UK |
| 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 Simvastatine Accord 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets from Accord Healthcare Ltd. The date of authorisation was on 22 November 2007 in the Netherlands.

The product is indicated for:

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1 of the SPC).

A comprehensive description of the indications and posology is given in the SPC. The indications and posology, as well as other aspects of the safe use of simvastatin have been discussed in the Directive 2001/83/EC art. 30 referral for Zocor, decided on by the European Commission on 28 April 2004.

Simvastine Accord contains simvastatin as active ingredient. Simvastatin is an inactive lactone (prodrug) that is hydrolysed in the liver to an active β-hydroxyacid form (β-hydroxy-simvastatin). β-Hydroxy-simvastatin is a HMG-CoA reductase inhibitor, it blocks the synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity. Simvastatine is intended as adjuvant with diet to decrease cholesterol and LDL-cholesterol in patients with hypocholesterolaemia.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Zocor 10, 20, 40 mg and 80 mg, film-coated tablets. In the Netherlands, Zocor 10, 20 and 40 mg tablets (NL license RVG 13193-5) have been registered by Merck Sharpe & Dohme B.V. since 5 December 1988. Zocor 80 mg (NL RVG 23457) has been registered since 29 June 1999. In addition, reference is made to Zocor authorisations in the individual member states (reference product).

Not all strenghts are applied for in all member states. The marketing authorisations are 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 a bioequivalence study in which the pharmacokinetic profile of the 80 mg product is compared with the pharmacokinetic profile of the reference product Zocor 80 mg tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their 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 generic 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 simvastatin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder which is practically insoluble in water, very soluble in methylene chloride and freely soluble in alcohol. No polymorphism is observed. It is an optically active compound.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP. Additional requirements for particle size and microbiological quality are included. 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 4 full-scale batches.

Stability of drug substance
The active substance is stable for 36 months. No special storage conditions are required. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

**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
Simvastatine Accord 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets contain as active ingredient 10, 20, 40 or 80 mg of simvastatin, respectively.

Simvastatine Accord 10 mg are light pink, round and biconvex film-coated tablets with “A” debossed on one side and “01” on the other side.
Simvastatine Accord 20 mg are light pink, round and biconvex film-coated tablets with the inscription “A” debossed on one side and “02” on the other side.
Simvastatine Accord 40 mg are pink, round and biconvex film-coated tablets with “A” debossed on one side and “03” on the other side.

Simvastatine Accord 80 mg are pink, capsule-shaped and biconvex film-coated tablets with “A” debossed on one side and “04” on the other side.

The film-coated tablets are packed in PVC/PE/PVdC/aluminium blisters. This resembles the packaging of the innovator tablets Zocor.

The excipients are:
*Tablet core* - butylated hydroxyanisole (E 320), ascorbic acid (E 300), citric acid monohydrate (E 330), microcrystalline cellulose (E 460a), pregelatinised maize starch, lactose monohydrate, magnesium stearate (E 470B).
*Film-coating* - hypromellose (E 464), hydroxy propyl cellulose (E 463), titanium dioxide (E 171), talc (E 553b), iron oxide yellow (E 172) (for 10/20 mg), iron oxide red (E 172) (for 10/20/40/80 mg).

The different tablets strengths are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients and packaging are usual for this type of dosage form. The clinical formulation and the biobatch are of the same qualitative and quantitative composition and produced in the same way as the commercial-scale batch. The comparative dissolution profiles of the tablets and the innovator product from several countries show comparable dissolution rates.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
First, granules are manufactured which are subsequently compressed into tablets. The tablets are coated, dried and packed. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for 8 full-scale batches.

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

Quality control of drug product
The product specification includes tests for appearance, identification, average weight, uniformity of dosage units, thickness, dissolution rate, water, assay, related substances, identification of colourants, residual solvents, assay of antioxidants and microbiological purity.
The release- and shelf life requirements are acceptable. The analytical methods have been adequately described and validated. Batch analysis results of two pilot-scale batches have been provided, demonstrating compliance with the specifications. The MAH committed to provide the Certificates of Analysis of the first three commercial batches.

Stability tests on the finished product
Stability data on the product have been provided for 10 full-scale batches (2 per strength) stored at 30°C/70% (36 months) and 40°C/75% (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC/PE/PVDC blister packaging sealed with aluminium foil.
No changes were seen in the tested quality parameters, except for related substances and anti-oxidant content. Related substances increase slightly and anti-oxidant content tends to decrease, but all results remain well within specification. The proposed shelf-life of 3 years could be granted. No special storage condition is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose, 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. Lactose monohydrate is derived from milk of healthy animals. A certificate on TSE/BSE-free quality of lactose has been provided.

## II.2 Non clinical aspects

This product is a generic formulation of Zocor, 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 identical products on the market. The approval of this product will not result in an increase in the total quantity of simvastatin 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Simvastatine Accord 80 mg (Accord Healthcare Ltd, UK) is compared with the pharmacokinetic profile of the British reference product Zocor 80 mg tablets (MSD, UK).

*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 in different member states.

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

*Design*
An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 64 (60 + 4 standby) healthy male subjects, aged 18-38 years. Each subject received a single dose (80 mg) of one of the 2 simvastatin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued until 4 hours after drug administration. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours after administration of the products.

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

*Analytical/statistical methods*
Plasma samples were analysed for the parent simvastatin and the metabolite hydroxy-simvastatin. 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.

*Results*

All 64 subjects completed the study. In accordance with the protocol, statistical evaluation included 60 subjects for $C_{max}$ and $AUC_{0-t}$. However, for statistical evaluation of the $AUC_{0-\infty}$ only 45 subjects were included for simvastatin and 35 subjects were included for hydroxy-simvastatin. This statistical evaluation of the MAH for $AUC_{0-\infty}$ did not include subjects with a "poor pharmacokinetic fit", and subjects for which terminal elimination half-life could not be established.

The RMS did not agree excluding subjects due to "poor pharmacokinetic fit". The data were included and evaluated. The statistical evaluation of $AUC_{0-\infty}$ included 58 subjects (for simvastatin) and 46 subjects (for hydroxy-simvastatin) for the ratio (Test/Reference). Determination of terminal elimination half-life was not possible for 2 subjects for simvastatin component and 14 subjects for hydroxy component due to absence of at least three non-zero concentrations in the terminal phase for calculation of pharmacokinetic parameters.

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

| **Treatment** | **$AUC_{0-t}$** ng.h/ml N=60 | **$AUC_{0-\infty}$** ng.h/ml N=58 | **$C_{max}$** ng/ml N=60 | **$t_{max}$** h N=60 | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 129.51 ± 71.72 | 164.66 ± 105.45 | 20.18 ± 11.94 | 2 ± 2.27 | - |
| **Reference** | 125.61 ± 69.01 | 162.78 ± 111.68 | 20.47 ± 15.01 | 2 ± 1.45 | - |
| ***Ratio (90% CI)** | 1.04 (0.94-1.15) | 1.05 (0.93-1.19) | 1.00 (0.90-1.10) | - | - |
| **CV (%)** | 32% | - | 34% | - | - |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**$t_{1/2}$** half-life | | | | | |

**ln-transformed values*

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

| **Treatment** | **$AUC_{0-t}$** ng.h/ml N=60 | **$AUC_{0-\infty}$** ng.h/ml N=46 | **$C_{max}$** ng/ml N=60 | **$t_{max}$** h N=60 | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 112 ± 80 | 177 ± 198 (n=50) | 10.2 ± 6.9 | 4.0 (0.7-12) | 15.1 ± 51 (n=50) |
| **Reference** | 110 ± 76 | 143 ± 119 (n=55) | 9.4 ± 6.4 | 4.0 (0.7-12) | 7.4 ± 4.1 (n=55) |
| ***Ratio (90% CI)** | 1.02 (0.94-1.10) | 1.12 (0.96-1.27) (n=46) | 1.07 (0.98-1.16) | - | - |
| **CV (%)** | 26 | 41 | 27 | - | - |

| | |
|---|---|
| **$AUC_{0-\infty}$** | 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*

The 90% confidence intervals calculated for simvastatin and hydroxy-simvastatin, the major active metabolite, for $AUC_{0-t}$ and $C_{max}$ were within the acceptance range of 0.80 – 1.25. The 90% confidence intervals calculated for simvastatin, for $AUC_{0-\infty}$ were within the acceptance range of 0.80 – 1.25 with and without inclusion of subjects with poor pharmacokinetic fit. For the $AUC_{0-\infty}$ of hydroxy-simvastatin it was shown that when subjects with "poor pharmacokinetic fit" were excluded from the statistical analysis, the 90% CI was within the acceptance range of 0.80 – 1.25. However, when these subjects were included, the 90% CI was outside the acceptance interval. The 90% CI calculated for $AUC_{0-\infty}$ for hydroxy-simvastatin, was difficult to interpret due to problems to characterize the terminal elimination phase. Therefore, it is proposed to ignore the $AUC_{0-\infty}$ of the hydroxy-metabolite, as the $AUC_{0-t}$ could be determined with far more precision, and the elimination phase does not contribute additional information with regard to absorption. The $AUC_{0-t}$ of hydroxy-simvastatin was well within the acceptation range. As expected a large intra-individual variation (CV) was seen.
Based on the pharmacokinetic parameters of simvastatin, supported by the data for hydroxy-simvastatin, it can be concluded that Simvastatine Accord 80 mg and Zocor 80 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.

*Extrapolation to different strengths*
The 10, 20, 40 and 80 mg tablets are produced by the same manufacturer in a similar process, the qualitative composition is similar, and ratios between amounts of active substance and ingredients are the same for the different tablet strengths. Simvastatin shows linear AUC profiles in response to different doses administered. Therefore, the results of the study with the 80 mg simvastatin tablets can be extrapolated to the 10, 20 and 40 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
Simvastatin was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of simvastatin 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**

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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections.
The test results demonstrate that several aspects of the leaflet should be improved. The suggestions for improvement are agreed by the RMS. However, the lay-out needs to be adapted to prevent the use of italics.
Furthermore, to improve findability of contraindicated medicines it is recommended to adapt the section '*Using other medicines*', as it would be logical that subjects would look in this section. In this section an

appropriate reference to the contraindications should be included and/or clearly stated in this section that these medicines are contraindicated.
Overall, it can be concluded that the readability of the leaflet is of an acceptable level.
The readability test itself and the evaluation report are of an acceptable quality. The conclusions are clear and concise.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Simvastatine Accord 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zocor 10, 20, 40 mg and 80 mg, film-coated tablets. Zocor 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 and are in agreement with other simvastatin containing products.

The Board followed the advice of the assessors. Simvastatine Accord 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets were authorised in the Netherlands on 22 November 2007.

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 Simvastatine 10, 20, 40 and 80 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 26 June 2008.

The first PSUR will be submitted with a Data Lock Point of November 2009. The second PSUR will then cover the period from November 2009 until April 2011 to synchronise with the European harmonised birth date (6 April 1988) and associated DLP, followed by 3-yearly submission of future PSURs.

The date for the first renewal will be: 4 December 2011

No post-approval commitments have been 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 |
| DLP | Data Lock Point |
| 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 |
| $t_{½}$ | 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 |
|---|---|---|---|---|---|---|
| Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release, not including batch control/testing. | NL/H/1314/ 001-004/IA/ 001 | IA | 2-10-2008 | 16-10-2008 | Approval | N |
| Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; All other manufacturing operations except batch release. | NL/H/1314/ 001-004/IB/ 002 | IB | 23-9-2008 | 20-10-2008 | Approval | N |
| Change in batch size of the finished product. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation. | NL/H/1314/ 001-004/IA/ 003 | IA | 23-9-2009 | 20-10-2008 | Approval | N |
| Chang or addition of imprints, bossing or other markings. | NL/H/1314/ 001-004/IA/ 004 | IA | 2-10-2008 | 16-10-2008 | Approval | N |
| Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a manufacturer currently approved. | NL/H/1314/ 001-004/IA/ 005 | IA | 10-12-2008 | 24-12-2008 | Approval | N |
| Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a new manufacturer. | NL/H/1314/ 001-004/IA/ 006 | IA | 10-12-2008 | 24-12-2008 | Approval | N |