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/1235/001-002/DC
Registration number in the Netherlands: RVG 101123-101124

28 October 2009

Pharmacotherapeutic group: selective serotonin reuptake inhibitors
ATC code: N06AB06
Route of administration: oral
Therapeutic indication: major depressive episodes
Prescription status: prescription only
Date of authorisation in NL: 2 July 2009
Concerned Member States: Decentralised procedure with DE, DK, ES, FI, NO and SE
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 Sertraline Bluefish 50 mg and 100 mg film-coated tablets, from Bluefish Pharmaceuticals AB. The date of authorisation was on 2 July 2009 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.

It is postulated that depressive disorders are associated with a disturbance of 5-hydroxytryptamine (serotonin) metabolism in the brain. It has been demonstrated in vitro that sertraline is a potent and selective inhibitor of neuronal reuptake of serotonin: this resulted in a potentiation of the physiological effects of the substance in animal models. Sertraline has only very weak effects on neuronal uptake of norepinephrine and dopamine. At clinically effective doses, sertraline inhibits the uptake of serotonin by human blood platelets.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zoloft 50 mg and 100 mg film-coated tablets (NL license RVG 16292 and 16293, respectively) which have been registered in the Netherlands by Pfizer B.V. since 1994. In Europe the active substance has been registered since 1990 under the brand name Lustral (Pfizer Ltd., UK). In addition, reference is made to Zoloft and Lustral authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokineti profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Lustral 100 mg tablets, registered in the United Kingdom. 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 a generic.
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 sertraline hydrochloride, a well-known active substance described in the European Pharmacopoeia (Ph. Eur*). The active substance is slightly soluble in water. It exhibits polymorphism (polymorphs I, II, III, IV and V). The active substance at issue is Form I, the most stable form at room temperature. Sertraline hydrochloride exhibits both geometrical and optical isomerism and the active pharmaceutical ingredient is the S-cis enantiomer.

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
Sertraline hydrochloride is manufactured in four steps. No class I organic solvents are used. The manufacturing process is well described and sufficiently validated.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. monograph, with additional requirements for residual solvents, bulk density, particle size and microbiological purity. 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 three production-scale batches.

Stability
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored.
No significant changes have been observed at batch storage conditions and the drug substance may be considered as very stable in the proposed packaging. The proposed retest period of two years without specific 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
Sertraline Bluefish 50 mg and 100 mg contain as active substance sertraline hydrochloride equivalent to 50 mg and 100 mg sertraline, respectively.
The 50 mg product is a white, capsule-shaped, film-coated tablet debossed with “A” on one side and score line in between “8” and “1” on the other side.
The 100 mg product is a white, capsule-shaped, film-coated tablet, debossed with “A” on one side and “82” on the other side.
The excipients used are:
*Tablet core* - calcium hydrogen phosphate dihydrate, microcrystalline cellulose, hydroxypropylcellulose sodium starch glycolate (Type A), magnesium stearate.
*Tablet coat* - opadry white OY-S-7355 containing: titanium dioxide (E171), hypromellose, macrogol 400, and polysorbate 80.

The film-coated tablets are packed in white opaque PVC-PVdC/Aluminium blister packs and PVC/Aluminium blister packs. The excipients and packaging are usual for this type of dosage form.

Both tablet strengths are qualitatively and quantitative fully dose proportional. All excipients comply with the Ph.Eur. Some additional in-house tests were proposed. Moreover, an acceptable specification has been provided for Opadry.

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. The quantitative composition of the drug product was varied and tested for dissolution. The dried compression approach was tried, but gave rise to problems which were overcome by using wet granulation. The choice of the manufacturing process and packaging was justified. The batches used in the bioequivalence study are acceptable. The excipients comply with the Ph. Eur. These specifications are acceptable. The pharmaceutical development of the product has been adequately performed.

Dissolution profiles have been submitted in the following media: 0.01N HCl, pH 4.5 acetate buffer and pH 6.5 phosphate buffer.

*For the products used in the bioequivalence study* - The dissolution profiles are comparable in the media 0.01N HCl, pH 4.5 buffer and pH 6.5 buffer for the 50 mg and 100 mg strengths.

*For the 50 mg tablet versus the 100 mg tablet* - For the 50 mg tablets no bioequivalence batch was used. However, dissolution information has also been provided for the biobatch, showing similarity with the 100 mg tablets. The dissolution profiles are comparable in all tested media (0.01N HCl, pH 4.5 and pH 6.5).

Additional dissolution profiles in pH 4.5 have been submitted for Sertraline tablets 50 and 100 mg compared with innovator tablets 50 and 100 mg from various EU countries. The dissolution profile of the 100 mg strength is similar to that of the BE, CZ, DK, FI, DE, EL, IE, PL and SE innovator products; the dissolution profile of the 50 mg strength is similar to that of the AT, CZ, DK, FI, DE, HU, IE, IT, NL, PL and SE innovator products.

**Manufacturing process**
The manufacturing process is a wet granulation process and consists of the following steps: sertraline hydrochloride, microcrystalline cellulose and sodium starch glycolate are mixed and granulated with a solution of hydroxypropyl cellulose. The granules are dried, milled and blended with calcium hydrogen phosphate and magnesium stearate. The final blend is compressed into tablets. Finally, the tablets are coated with Opadry coating. Sufficient information on the manufacturing process and its relevant parameters has been provided.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for full-scale batches.

**Quality control of drug product**
The product specification includes tests for appearance, identity, average mass, thickness, uniformity of dosage units, dissolution, assay, related substances, identity of colorants and microbiological purity. The release and shelf-life requirements are identical except for dissolution and assay. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.
Stability tests on the finished product
Stability data on the product has been provided for two pilot-scale batches per strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Results of commercial-scale batches are awaited. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PVdC/Al blisters and PVC/Al blisters.
No out of specification for any parameter has been observed. The proposed shelf life of 36 months could be granted with no specific storage condition. The MAH has committed to report any significant changes occurring during the stability studies on commercial batches.

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.

II.2 Non clinical aspects
These products are generic formulations of Zoloft 50 mg and 100 mg film-coated tablets, which are 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 products are intended as a substitute for other identical products on the market. The approval of these products will not result in an increase in the total quantity of sertraline 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
Sertraline 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 Sertraline Bluefish 100 mg film-coated tablets (Bluefish Pharmaceuticals AB, Sweden) is compared with the pharmacokinetic profile of the reference product Lustral 100 mg tablets (Pfizer Ltd., 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.

Study design
An open-label, randomised, two treatment, two sequence, two period, two-way cross-over bioequivalence study was carried out under fasted conditions in 28 healthy male volunteers. The results of 24 subjects were to be evaluated. Twenty-six subjects received the test formulation and 27 the reference formulation. The tablets were orally administrated with 240 ml after an overnight fast of 10 hours. Lunch was served 4 hours upon administration of the tablets. There were 2 dosing periods, separated by a washout period of 14 days.
Blood samples were collected predose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 48, 72, 96, 120 and 144 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.
Sertraline may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sertraline. 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

One subject did not show up in the second period. Another subject did not meet the inclusion criteria. In addition, one subject vomited within 2 times the median \( t_{\text{max}} \). These three subjects were withdrawn from the study. As per protocol, 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of sertraline 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>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1130 ± 370</td>
<td>1191 ± 405</td>
<td>30.2 ± 9.6</td>
<td>8.0 (4 – 11)</td>
<td>30.1 ± 6.6</td>
</tr>
<tr>
<td>Reference</td>
<td>1107 ± 424</td>
<td>1166 ± 461</td>
<td>29.7 ± 9.7</td>
<td>7.0 (6 – 16)</td>
<td>30.4 ± 5.6</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.04 (0.98 – 1.10)</td>
<td>1.04 (0.98 – 1.10)</td>
<td>1.02 (0.94 – 1.11)</td>
<td>---</td>
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<tr>
<td>CV (%)</td>
<td>11.6</td>
<td>11.2</td>
<td>17.6</td>
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</tr>
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</table>

*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 sertraline under fasted conditions, it can be concluded that Sertraline Bluefish 100 mg film-coated tablets and Lustral 100 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 bioequivalence results

A biowaiver for the 50 mg tablet was requested. This is an acceptable approach for a generic application. The results of the bio-equivalence study can be extrapolated to the 50 mg tablet strength, since the criteria for a biowaiver as mentioned in the CPMP guideline “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98), are met. The 50 mg and 100 mg strengths are manufactured by the same manufacturer and using the same manufacturing process, the qualitative composition is the same, the strengths are dose-proportional, the dissolution profiles are similar and the pharmacokinetics have been shown to be linear over the therapeutic range.

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

Sertraline was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of sertraline 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. Testing was performed with a total of 20 participants of whom 10 were included in each of the two rounds of user testing. The 20 participants included were recruited from a database.
The questionnaire was developed by determining the 17 most important points of information relating to specific safety and compliance issues. A sufficient number of questions have been developed testing “findability”, “understandability” and “applicability”, i.e. can the patient find the information quickly and easily, can he/she understand it and act on it appropriately.

Based on the results of the readability testing (for one question the criteria as set in the readability guideline were not met), the MAH proposed some amendments to the PIL in order to improve readability. Although not re-tested, the amendments made were found acceptable and can be considered an improvement to the PIL. Overall, the report is of sufficient quality and the results show that the PIL fulfils the criteria as set in the readability guideline.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sertraline Bluefish 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zoloft 50 mg and 100 mg film-coated tablets. Zoloft 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 sertraline containing products.

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 Sertraline Bluefish film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 December 2008. Sertraline Bluefish 50 mg and 100 mg film-coated tablets were authorised in the Netherlands on 2 July 2009.

A European harmonised birth date has been allocated (1 March 1990) and subsequently the first data lock point for sertraline is March 2011. The first PSUR will cover the period from December 2008 to March 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 November 2011

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

Quality - drug product
- Stability data on the product has been provided for two pilot-scale batches per strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Results of commercial-scale batches are awaited.
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<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&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<tr>
<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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<tr>
<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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<tr>
<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&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
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<th>Scope</th>
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<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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<tr>
<td>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.</td>
<td>NL/H/1235/001-002/IA/001</td>
<td>IA</td>
<td>26-8-2009</td>
<td>14-9-2009</td>
<td>Approval</td>
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