

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml
and 0.5 mg/ml, solution for injection
Sandoz B.V., the Netherlands**

octreotide acetate

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/1998/001-004/MR

Registration number in the Netherlands: RVG 32592, 32593, 34198, 32594

24 February 2011

Pharmacotherapeutic group:	hypothalamic hormones, antigrowth hormones
ATC code:	H01CB02
Route of administration:	intravenous; subcutaneous
Therapeutic indication:	symptomatic treatment and reduction of plasma levels of growth hormone (GH) and IGF-1 in patients with acromegaly who respond inadequately to treatment with surgery or radiotherapy (see next page); relief of symptoms associated with functional gastroenteropancreatic endocrine tumours; prevention of complications after pancreatic surgery; acute treatment of bleeding oesophageal varices in patients with cirrhosis
Prescription status:	prescription only
Date of first authorisation in NL:	8 December 2008
Concerned Member States:	Mutual recognition procedure with BE, BG, PL, PT
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 Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml, solution for injection from Sandoz BV. The date of authorisation was on 8 December 2008 in the Netherlands.

The product is indicated for:

- Symptomatic treatment and reduction of plasma levels of growth hormone (GH) and IGF-1 in patients with acromegaly who respond inadequately to treatment with surgery or radiotherapy. Octreotide may also be administered to patients with acromegaly who are not able or willing to undergo surgery, or in the initial stage of radiotherapy treatment until it becomes effective.
 - Relief of symptoms associated with functional gastroenteropancreatic endocrine tumours:
 - carcinoids with the characteristics of the carcinoid syndrome
 - VIPomas
 - glucagonomas
 - gastrinomas/Zollinger-Ellison syndrome, usually in combination with proton pump inhibitors or H2-blockers
 - insulinomas, for the preoperative control of hypoglycaemia and as maintenance therapy
 - GRFomas
- Octreotide is not an anticancer agent and is not curative in the above-mentioned patients.
- Prevention of complications after pancreatic surgery
 - Acute treatment of bleeding oesophageal varices in patients with cirrhosis, in order to stop the bleeding or prevent recurrent bleeding. Octreotide must be used in combination with an appropriate therapy such as endoscopic sclerotherapy.

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

Octreotide contains octreotide, a synthetic octapeptide derivative of the naturally occurring somatostatin. The pharmacological effects are similar, but the duration of action is considerably longer. It inhibits pathologically increased secretion of peptides and serotonin in the gastroenteropancreatic (GEP) endocrine system and of the growth hormone (GH). In contrast to somatostatin, octreotide inhibits the GH-secretion better than insulin secretion, and octreotide administration is not followed by a rebound hypersecretion of hormones (such as GH in patients with acromegaly).

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Sandostatin 50 µg/ml, solution for injection which has been registered in Denmark by Novartis Healthcare A/S since 1988. In the Netherlands, the innovator products Sandostatine 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml solution for injection (NL License RVG 12612-12614, 14997) have been registered since 28 March 1989 (0.05, 0.1, 0.2 mg/ml) and 12 October 1990 (0.5 mg/ml) by Novartis Pharma B.V. In addition, reference is made to Sandostatin 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. As Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml, solution for injection are products for parenteral use in aqueous solution, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current 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 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 octreotide, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white, amorphous powder, which is soluble in water and acetic acid. Octreotide acetate is not crystalline

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

Octreotide acetate is prepared via a stepwise solid phase synthesis in 8 steps. The starting materials are adequately characterized. TSE and viral safety have been confirmed.

Quality control of drug substance

The specification parameters are acceptable in view of the route of synthesis and the various ICH guidelines. As described in the provisions in 5.10 of the Ph.Eur., peptides do not necessarily have to comply with the general monograph 'Substances for pharmaceutical use'. The general concepts of reporting, identification and qualification of impurities are however equally valid for these classes.

The identified impurities have been toxicologically assessed. The proposed limits are acceptable, as well as the set limits for unidentified impurities and total impurities. The limits for residual solvents have also been sufficiently justified. Batch analytical data demonstrating compliance with this specification have been provided for 8 batches.

Stability of drug substance

Stability data have been obtained during storage at -20°C±2°C and 2-8°C (both up to 36 months), and 25°C/60% RH (6 months). The drug substance was packaged in the commercial packaging. The stability data presented fully support the claimed retest period of 12 months for the drug substance when stored at -20°C ± 2°C.

* 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

The different Octreotide Sandoz strengths contain octreotide acetate corresponding to 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml octreotide, and are clear and colourless solutions with pH 3.9 - 4.2 and osmolarity 300 - 360 mOsmol/kg.

The excipients are: lactic acid (E 270), mannitol (E 421), sodium hydrogen carbonate (E 500), water for injections and phenol (0.2 mg/ml only).

The solution for injection is packed in colourless type I glass ampoules (0.05, 0.1, 0.5 mg/ml) and vials (0.2 mg/ml). The ampoules contain 1 ml of solution and are intended for single use. The vials of 0.2 mg/ml product contain 5 ml solution; this container is intended for multiple use and is conserved with phenol. The vials are closed by a bromobutyl rubber stopper and aluminium crimp cap.

Pharmaceutical development

The development of the product was satisfactorily performed and explained. The excipients used are common in the manufacture of parenteral formulations and are also present in the innovator product. Nitrogen is used to displace air from the solution subject to oxidation and to replace air in the headspace above the product. The proposed packaging materials are usual and suitable for the product at issue.

Microbiological attributes

Sterility is tested appropriately in accordance with Ph.Eur. requirements. For the multidose vials, phenol is used as a preservative. The inclusion of a preservative agent is acceptable as the product is intended for multiple use and consists of an aqueous solution. Phenol is also present in the innovator composition. The concentration of 0.5% is in line with the USP *Handbook of Excipients* and with the innovator. Release testing has been performed in accordance with the Ph.Eur. and the results comply with the requirements as specified in the monograph. Ph.Eur. compliant testing on antimicrobial effectiveness has been performed on three batches after 40 months of storage at 2-8°C. The MAH has sufficiently shown the efficacy of antimicrobial preservation.

Manufacturing process

The drug product is prepared by dissolution of the excipients and the active substance. Adequate limits for pH and isotonicity are set. The product is sterilized by filtration. It was shown that the active substance is thermo labile, therefore sterile filtration is acceptable. This sterilization process has been sufficiently validated for all four products by calculation of the Theoretical Reduction Factor. Appropriate in-process controls have been set. The manufacturing process has been validated for three batches of the 0.05, 0.1 and 0.5 mg/ml strengths. An appropriate protocol has been provided for process validation of the first three consecutive batches of 0.2 mg/ml vials.

Overages and overfill

For the ampoules no overage or overfill is applied. The finished product specification does however include the requirement for extractable volume, so at least the nominal volume is present. However, the 5 ml vials intended for multiple use are filled with a technical overage of 0.6 ml: up to 5.6 ml. This overage is based on calculation of the average loss in case of repeated removal of solution from the vial. The proposed overfill is acceptable.

Control of excipients

All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, appearance, extractable volume, identity, assay, impurities, pH, (sub-)visible particles, sterility, endotoxins and uniformity of dosage units. For the 5 ml presentation, additional tests for identification and assay of phenol have been included. All parameters are acceptable. The proposed release and shelf life limits are identical and acceptable. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data have been provided on two batches of the 0.05, 0.1 and 0.5 mg/ml strengths and three batches of the 0.2 mg/ml strength. The results demonstrate compliance with the specification.

Stability of drug product

The drug products have been stored at 2-8°C and 25°C/60% RH. At 2-8°C the ass is stable and the content of impurities does not increase. Degradation is observed at 25°C. The product is also shown to be sensitive to light.

Based on the results provided, the proposed shelf-life of 4 years for the 0.05/0.1/0.5 mg/ml products was granted. The storage conditions are 'store in the outer carton to protect from light' and 'do not freeze'. For the 0.2 mg/ml strength, which contains a preservative, the MAH has demonstrated the efficacy of the antimicrobial preservative at the end of shelf life (40 months). The proposed shelf-life of 3 years, stored at 2-8°C could therefore be granted. The storage conditions are the same as for the other strengths: 'store in the carton to protect from light' and 'do not freeze'.

Compatibility /In-use stability

Compatibility of the product with glucose 5% and NaCl 0.9% has been shown. In section 6.6 of the SPC it is however advised to preferably use a NaCl solution in view of the effects of octreotide on homeostasis. This is in line with the statements in the SPC of the innovator, and is therefore acceptable.

The SPC prescribes the dilution of 0.5 mg/ml ampoule (any strength) with 60 ml infusion liquid. The total infusion period is 1 – 5 days. An infusion speed of 3 ml/hour would be applicable for the tested dilution. The total of 60 ml would be infused in 20 hours. The compatibility during this period has sufficiently been demonstrated. It is furthermore noted, that the compatibility claims are in line with those of the innovator products (0.05 mg/ml to 0.5 mg/ml). The claim is therefore sufficiently justified.

The in-use stability of the vials has been tested. Chemical and physical stability has been demonstrated for 14 days at temperatures below 25°C.

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. No risk is present as the materials are of plant or synthetic origin.

II.2 Non-clinical aspects

This product is a generic formulation of Sandostatin, 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 octreotide 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

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

Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml, solution for injection are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of their reference product.

Risk management plan

Octreotide was first approved in 1988 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of octreotide 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 mutual recognition procedure is in accordance with that accepted for the reference product Sandostatin.

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 two rounds with a total of 22 participants. Participants were asked 15 questions regarding the content of the package leaflet. Participants could also give their opinion on the leaflet text and layout in general.

After the first round the leaflet was amended according to the recommendations. The second round was performed on the amended leaflet.

The report of the readability test states that the package leaflet was considered to be too extensive. The recommendations to concise the leaflet have been adopted. As the adjusted PIL has been successfully tested, the changes are considered acceptable. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml, solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Sandostatin. Sandostatin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 octreotide containing products.

The Board followed the advice of the assessors. Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml, solution for injection were authorised in the Netherlands on 8 December 2008.

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 Octreotide Sandoz 0.05 mg/ml, 0.1 mg/ml, 0.2 mg/ml and 0.5 mg/ml with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 6 December 2010.

A European harmonised birth date has been allocated (23 June 1995) and subsequently the first data lock point for octreotide is June 2011. The first PSUR will cover the period from December 2010 to June 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 24 March 2012.

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