CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Estradiol Sandoz tablet 2 mg, film-coated tablets
Sandoz B.V., the Netherlands

estradiol hemihydrate

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/0685/001/MR
Registration number in the Netherlands: RVG 26359

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Pharmacotherapeutic group:	Natural and semisynthetic estrogens, plain
ATC code:	G03CA03
Route of administration:	oral
Therapeutic indication:	Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women; prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.
Prescription status:	prescription only
Date of authorisation in NL:	25 November 2002
Concerned Member States:	Mutual recognition procedure with DE, DK, EE, FI, FR, LT, LU, LV, SK
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 concerned member states have granted a marketing authorisation for Estradiol Sandoz tablet 2 mg, film-coated tablets, from Sandoz B.V, the Netherlands. The date of authorisation was on 25 November 2002 in the Netherlands. The product is indicated for hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women. After marketing authorisation a second indication (*Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis*) was added by a type II variation (see table 'Steps taken after finalisation of the initial procedure' on page 8).

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

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to the endogens human female sex hormone estradiol. It substitutes for the loss of oestrogen production in menopausal women and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

This application concerns a generic application claiming essential similarity with the innovator product Estrofem®, 2 mg tablets (NL License RVG 09810) which has been registered in the Netherlands by Novo Nordisk since 1984. In addition, reference is made to Estrofem® 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 pharmacokinetic 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 Estrifam®, registered in Germany. Estrifam® is the trade name for the innovator product in Germany, which is identical with the innovator product on the Dutch market. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture has 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.

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 and excipients
The active substance is estradiol hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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. Estradiol hemihydrate is a white or almost white powder or colourless crystals. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

The CEP procedure is used for the active substance. Under this 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 suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months when stored in original package without special storage conditions.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for indigotine. For indigotine reference is made to the French Pharmacopoeia.

Medicinal Product

Composition
Estradiol Sandoz tablet 2 mg, film-coated tablets contain 2.07 mg estradiol hemihydrate, corresponding to 2 mg estradiol and are blue, round tablets with a score line on one side.

The film-coated tablets are packed in Aluminium/Polyvinylchloride blisters.

The excipients are:
Tablet core: microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, colloidal anhydrous silica
Tablet coat: aluminium hydroxide, hypromellose, indigotine (E 132), lactose monohydrate, macrogol 4000, titanium dioxide (E 171)

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Estrofem®.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 2 production scale batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, identification, resistance to crushing, mean weight, content uniformity, uniformity of mass, disintegration, dissolution rate, assay, related substances and microbiological impurity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods has been provided.

Batch analytical data for 5 production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product has been provided for 5 batches in accordance with applicable European guidelines demonstrating the stability of the product over 3 years. No specific storage conditions need to be included in the SPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of the originator product Estrofem which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone pre-clinical 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 estradiol hemihydrate 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

Estradiol hemihydrate is a well known active substance with established efficacy and tolerability.

The indication *Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women* was acceptable for all concerned member states. However during the procedure a potential serious risk to public health was raised regarding one indication in the SPC: *Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis*, which was not approvable for all concerned member states. Therefore, a referral to the CMD(h) was started.

In the CMD(h) meeting of May 2006, the following was discussed:
A concern was raised by one member state regarding the indication *Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis*, as the dosage and the indication is not included in the SPC of the reference product Estrofem, marketed by Novo Nordisk in that particular concerned member state. At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed. Following the discussion, agreement was reached to add the indication via a type II variation, see table 'Steps taken after finalisation of the initial procedure' on page 8).

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Estradiol Sandoz tablet 2 mg is compared with the

pharmacokinetic profile of the German reference product Estrifam®. Both products contain 2 mg of estradiol.

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.

A randomised, single-dose, open, 2-way cross-over bioequivalence study was carried out under fasted conditions in 20 healthy postmenopausal female subjects, aged 52-70 years. Each subject received 4 mg estradiol of one of the two estradiol formulations. Two tablets were orally administered with 150 ml water after an overnight fast. A standard lunch and diner were served after the 4 and 12 hour blood sampling time points respectively. Prior dosing blood samples were collected for estradiol level determination. Blood samples were collected over a period of 96 hours (17 sampling points). All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Estradiol Sandoz tablet 2 mg was compared to the German reference product Estrifam®, 2 mg tablet, Novo Nordisk.

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

Treatment N=22	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4.92 ± 1.52	5.56 ± 1.78	139 ± 40.1	8.75	26.2 ± 7.7
Reference	4.49 ± 1.67	5.22 ± 1.80	139 ± 46.1	10.0	29.6 ± 21.2
***Ratio (90% CI)**	1.10 (0.97-1.23)	1.05 (0.93-1.18)	1.01 (0.91-1.12)	--	--
CV (%)	20.8	21.9	18.3	--	--

$AUC_{0-\infty}$ 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*

Estradiol should be taken once daily without reference to food intake. Therefore, 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 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 estradiol under fasted conditions, it can be concluded that Estradiol Sandoz tablet 2 mg and the German reference product Estrifam® are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing, only the composition of the coating suspension was slightly different. This was considered acceptable.

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

Estradiol was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of estradiol hemihydrate can be considered to be well established and no other product specific pharmacovigilance issues were identified pre- or post

authorisation than already 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.

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 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Estradiol Sandoz tablet 2 mg, film-coated tablets, has a proven chemical-pharmaceutical quality and is a generic form of Estrofem®. Estrofem 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 SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Estradiol Sandoz tablet 2 mg was authorised in the Netherlands on 25 November 2002.

In the CMD(h) meeting of May 2006, the following was discussed:
The indication *Prevention of osteoporosis in postmenopausal women at high risk of fractures who are intolerant or contraindicated for other medicinal products approved for the prevention of osteoporosis* is beyond the indications approved for the reference product in one concerned member state. The CMD(h) agreed to finalise the procedure without the osteoporosis indication, together with the commitment of the MAH to apply for this indication via a type II variation. After marketing authorisation the second indication was added by a type II variation (see table Steps taken after finalisation of the initial procedure at Page 8). This variation procedure was finalised at 18 January 2007.

The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Estradiol Sandoz tablet 2 mg with the reference product, and have therefore granted a marketing authorisation.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from September 2006 until September 2009.

The date for the first renewal will be: 2 May 2011.

The following post-approval commitments have been made during the procedure:
- The MAH committed to submit a type II variation to apply for the indication *Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.* This indication was approved (See table Steps taken after finalisation of the initial procedure at Page 8).

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
HRT	Hormone Replacement Therapy
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
PL	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 procedure	Approval/ non approval	Assessment report attached
Addition of the indication *Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.*	NL/H/0685/ 001/II/001	Type II; post-approval commitment	24-7-2006	18-1-2007	Approval	N
Change in the name of the medicinal product in FR only.	NL/H/0685/ 001/IB/002	IB	23-11-2006	3-1-2007	Approval	N
Change in the name of the medicinal product in NL only.	NL/H/0685/ 001/IB/003	IB	22-11-2006	3-1-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/0685/ 001/IA/004	IA	28-11-2007	12-12-2007	Approval	N
Name change of a CEP holder.	NL/H/0685/ 001/IA/005	IA	1-7-2008	15-7-2008	Approval	N