CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fluconazol Novopharm 2 mg/ml solution for infusion
Novopharm Ltd, United Kingdom

fluconazole

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/1013/01/MR
Registration number in the Netherlands: RVG 27719

1 December 2009

Pharmacotherapeutic group:	antimycotics for systemic use: triazole derivatives
ATC code:	J02AC01
Route of administration:	intravenous
Therapeutic indication:	treatment of mycoses caused by *Candida* and other susceptible yeasts (adults and children); treatment of mycoses caused by *Cryptococci* (adults only)
Prescription status:	prescription only
Date of first authorisation in NL:	17 December 2003
Concerned Member States:	Mutual recognition procedure with BE, CY, DE, EL, IE, LU
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 Fluconazol Novopharm 2 mg/ml solution for infusion, from Novopharm Ltd. The date of authorisation was on 17 December 2003 in the Netherlands.

The product is indicated in adults and children for treatment of mycoses caused by *Candida* and other susceptible yeasts, in particular:

- Systemic candidiasis (including disseminated deep infections and peritonitis)
- Severe mucosal candidiasis (including oropharyngeal candidiasis, oesophageal candidiasis and non-invasive bronchopulmonary candidiasis), where oral treatment is not possible.

In aldults only, the product is indicated for treatment of:

- mycoses caused by *Cryptococci,* in particular Cryptococcal meningitis.
- Prophylaxis against deep *Candida* infections (especially *Candida albicans*) in patients with neutropenia due to bone marrow transplantation.

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

Fluconazole is a member of the triazole class of antifungal agents with primarily fungistatic effects. It is a potent and selective inhibitor of the synthesis of fungal ergosterol which leads to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Diflucan i.v. 2 mg/ml solution for infusion (NL RVG 14769) which has been registered in the Netherlands by Pfizer B.V. since 1991. In addition, reference is made to Diflucan i.v. 2 mg/ml 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 Fluconazol Novopharm 2 mg/ml solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current 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.

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 fluconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white crystalline powder, slightly soluble in water, and freely in methanol. Information has been provided concerning solubility in other solvents, the pH in water, and pKa values. The substance is a racemic mixture. Two crystalline polymorphic forms exist. The manufacturing method results in the formation of only "form 2", which is confirmed in every batch by testing.

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
The manufacturing process is adequately described in the DMF. The process yields fluconazole that easily complies with the Ph.Eur. requirements.

Specification
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.

Stability
Stability data on the active substance have been provided for 13 batches in accordance with applicable European guidelines stored at 40ºC/75%RH (up to 6 months) and 25ºC/60%RH (up to 36 months). The samples were packaged in the commercial packaging. The batches are very stable during 36 months under long term conditions and 6 months under accelerated conditions. No change is observed in any of the parameters. The stability data justify the proposed 48-month re-test period: 12 months of extrapolation were added. No temperature/humidity storage conditions need to be specified.

** 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
Fluconazol Novopharm 2 mg/ml contains as active substance 2 mg per ml of fluconazole, and is a clear and colourless solution.

The solution for infusion is packed in clear type I glass bottles, closed with a bromobutyl rubber stopper and aluminum cap. The solution will be marketed in bottles containing 25, 50, 100 and 200 ml.

The excipients are: water for injections, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

Pharmaceutical development
The objective was to develop a product similar to the innovator product Diflucan i.v. 2 mg/ml. Bioequivalence can be assumed, for the products are aqueous solutions in the same pharmaceutical form and they have the same qualitative and quantitative composition. Compatibility tests at room temperature

were performed with mixtures of the test product with different diluents. The development of the product is described, the choice of excipients is justified and their functions are explained. The excipients are normal for the dosage form, and are used in normal amounts. All excipients comply with their Ph.Eur. monograph.

Compatibility with diluents and dosage devices
Compatibility at room temperature is confirmed with mixtures of the test product with each of the following diluents:
- dextrose 20%
- lactated Ringer's solution
- Hartmann's solution
- potassium chloride 0.18% in dextrose 4.3%
- sodium bicarbonate 4.2%
- sodium chloride 0.9%.

The diluents used in the test are the fluids mentioned as compatible in the SPC, which is the same as the innovator SPC in this respect.

Manufacturing process
The manufacturing process has been described in sufficient detail. There are no "intermediates" in the formal sense; the production process continues without waiting times and is completed in one day. Twelve production batches were made in the course of validation studies: three of each volume. Appropriate critical steps were identified and shown to be under satisfactory control.

Control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, specific gravity, pH, osmolality, volume variation, identification, assay, sterility, bacterial endotoxins, related substances, vial tightness, particles, container integrity and packaging. The pH, osmolality, endotoxins, sterility, and particles are determined with Ph.Eur. test methods. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 12 batches - 3 of each volume - have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
During the MRP, stability data on the product were provided for 3 full scale batches of each volume in accordance with applicable European guidelines. The batches were stored at 25ºC/60% RH (up to 60 months) and 40ºC/75% RH (up to 6 months). The samples were packaged in the proposed bottles. The observed increase of the levels of some impurities is barely detectable and it appears to stop after 24 months. Based on the stability data the claimed shelf-life of 36 months (25, 50, 100 ml) and 24 months (200 ml) was granted. The labelled storage conditions are *"do not refrigerate or freeze"*. The in-use stability has not been tested. The product is to be administered without delay after the stopper is pierced.
After finalisation of the MRP, the shelf-life has been changed by a type IB variation (NL/H/1013/001/IB/002) to 5 years for each volume on 15 May 2008. See also table 'Steps taken after the finalisation of the initial procedure – Summary' on Page 8.

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

This product is a generic formulation of Diflucan i.v. 2 mg/ml solution for infusion, 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 fluconazole 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

Fluconazol Novopharm 2 mg/ml solution for infusion is a parenteral formulation and therefore fulfils 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 Fluconazol Novopharm 2 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 product can be used instead of its reference product.

Risk management plan

Fluconazole was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fluconazole 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

SPC

The SPC assessment was based on the innovator product Diflucan in the Netherlands. The chemical-pharmaceutical sections of the Dutch SPC are an adequate reflection of these product characteristics, otherwise the SPC is in line with the innovator SPC.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot study of two interviews and two test rounds. Both test rounds were done with 10 subjects.

The questionnaire included one general question, 22 specific questions on the content of the PIL and five questions to gain a general opinion of the subject's interpretation of the PIL. The answers to these last questions were not used in the assessment procedure. A sufficient number of questions have been used testing "traceability", "comprehension"and "applicability", i.e. can the patient find the information quickly and easily, can he/she understand it and act on it appropriately.

Adults of either sex were recruited, although there were more female than males participants as local hospital showed that 90% of prescribing for fluconazole was for females and 10% for males.

The first test lead to the following major results: Overall, 91.7% of the questions were successfully located and the information was understood very easily or easily by the participants. The first round showed that participants experienced some difficulty with three specific questions. For the second phase, one of these questions was reworded. The other two did not lead to any revision.

In the second round, the questions that were successfully located and understood increased to 93.5%.

The participants experienced some difficulty in understanding the section "important information about some of the ingredients in Fluconazole i.v. 2 mg/ml", due to the term sodium chloride. Not all of the subjects did know that sodium chloride was salt. It was proposed to amended the section as follows

"If you are on a low sodium (salt) diet tell your doctor, pharmacist or nurse before they give you Fluconazole Infusion".

There were sufficient questions about the critical sections. The member states are of the opinion that the readability of the package leaflet is sufficient taking into account the results of the test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fluconazol Novopharm 2 mg/ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Diflucan i.v. 2 mg/ml solution for infusion. Diflucan i.v. 2 mg/ml 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other fluconazole containing products.

This product is only intended for administration by healthcare professionals. Therefore it is not required to put the name of the product in Braille on the packaging.

The Board followed the advice of the assessors. Fluconazol Novopharm 2 mg/ml solution for infusion was authorised in the Netherlands on 17 December 2003.

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 Fluconazol Novopharm 2 mg/ml with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 25 October 2007.

A European harmonised birth date has been allocated (3 March 1988) and subsequently the first data lock point for fluconazole is March 2011. The first PSUR will cover the period from October 2007 to March 2008, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 25 October 2012.

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

Quality - medicinal product

- The MAH committed to perform stability studies on three full-scale batches of each strength for 60 months using the protocol described in the dossier.

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
$t_{½}$	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
Addition of an alternative secondary packaging site of the finished product.	NL/H/1013/ 001/IA/001	IA	10-4-2008	24-4-2008	Approval	N
Shelf life changes to 5 years.	NL/H/1013/ 001/IB/002	IB	15-4-2008	15-5-2008	Approval	N
Registration of an alternative finished product manufacturer of Fluconazol 100mg/50ml, 200 mg/100 ml & 400 mg/200 ml solution for Infusion, with a consequential increase in batch size.	NL/H/1013/ 001/II/003	II	18-6-2008	17-8-2008	Approval	N
Change in the name of the medicinal product	NL/H/1013/ 001/IB/004	IB	17-2-2009	19-3-2009	Approval	N
Addition of an alternative finished product manufacturer with a consequential change in batch size.	NL/H/1013/ 001/II/005	II	27-1-2009	7-7-2009	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance; from a new manufacturer (replacement or addition); other substances.	NL/H/1013/ 001/IA/006	IA	6-10-2009	20-10-2009	Approval	N