

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules
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/1017/001-004/MR
Registration number in the Netherlands: RVG 27715-27718

12 January 2010

Pharmacotherapeutic group:	antimycotics for systemic use: triazole derivatives
ATC code:	J02AC01
Route of administration:	oral
Therapeutic indication:	acute and recurrent vaginal candidiasis; oropharyngeal candidiasis; oesophageal candidiasis; deep-seated systemic candidosis; prophylaxis against <i>Candida</i> infections after bone marrow transplantation or radiotherapy; recurrence prevention of oropharyngeal candidosis in patients with AIDS; cryptococcal meningitis; Maintenance treatment for the prevention of cryptococcal meningitis in patients with AIDS.
Prescription status:	prescription only
Date of first authorisation in NL:	17 December 2003
Concerned Member States:	Mutual recognition procedure with BE, LU, CY, IT and EL (200 mg only)
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 Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules, from Novopharm Ltd. The date of authorisation was on 17 December 2003 in the Netherlands.

The product is indicated for:

- treatment of acute and recurrent vaginal candidiasis when systemic therapy is considered appropriate.
- treatment of oropharyngeal candidiasis also in the case of immunity disorders caused by malignancy or Acquired Immune Deficiency Syndrome (AIDS).
- treatment of oesophageal candidiasis also in patients with immunodeficiency disorders such as patients with Acquired Immune Deficiency Syndrome (AIDS).
- treatment of deep-seated systemic candidosis.
- as a prophylaxis against *Candida* infections in patients with neutropenia following bone marrow transplantations or following cytotoxic chemotherapy or radiotherapy.
- recurrence prevention of oropharyngeal candidosis in patients with AIDS.
- cryptococcal meningitis e.g. in patients with AIDS, in patients undergoing transplantations, or in patients with other causes of immunosuppression and in normal hosts.
- maintenance treatment for the prevention of relapses of cryptococcal meningitis in patients with AIDS.

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 products Diflucan 50, 100, 150 and 200 mg capsules (NL License RVG 13038, 14767, 13039, and 14768, respectively) which have been registered in the Netherlands by Pfizer B.V. since 23 January 1990 (50 and 150 mg) and 19 September 1991 (100 and 200 mg). In addition, reference is made to Diflucan 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 Diflucan 200 mg capsules, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. 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 application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is 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/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.

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 40°C/75%RH (up to 6 months) and 25°C/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

The products are immediate release, hard gelatin capsules filled with a mixture of the active substance and a number of excipients. The capsule shells are coloured, the four strengths can be distinguished by their colour:

Fluconazole "Novopharm" 50 mg is a green-white capsule, size number 2.

Fluconazole "Novopharm" 100 mg is a buff-buff capsule, size number 1.

Fluconazole "Novopharm" 150 mg is a yellow capsule, size number 0.

Fluconazole "Novopharm" 200 mg is a white capsule, size number 0.

The capsules are packed in PVC/Aluminium foil blisters.

The excipients are:

Capsule content - lactose monohydrate, microcrystalline cellulose (E460), maize starch, colloidal silicon dioxide (E551), magnesium stearate (E 470b) and sodium lauryl sulphate.

Capsule shell - titanium dioxide (E171) and gelatin.

Colorants - 50 mg: quinoline yellow (E104), iron oxide yellow (E172), patent blue V (E131). 100 mg: iron oxide yellow (E172). 150 mg: quinoline yellow (E104), sunset yellow (E110).

The contents of the capsules are dose proportional.

Pharmaceutical development

The development of the product is described, the choice of excipients is justified and their functions have been explained. A standard hard gelatin capsule formulation was chosen. Pre-formulation studies showed that it was suitable. The reference products have the same type of formulation.

The *in vivo* bioequivalence studies for the NL marketing authorisation were performed with Fluconazole "Novopharm" capsules (200 mg) and Diflucan UK capsules 200 mg. The compositions of the UK and the Dutch Diflucan products are comparable to such a degree that the results of the bioequivalence study are applicable to the Dutch originator product as well. The 200 mg capsules have a dissolution profile that is comparable with the dissolution profiles of the tested CMS innovator products. Comparative dissolution studies were performed with innovator capsules from each CMS. Batches of every available strength were used. The results of the tests were analysed statistically. The similarity factors that resulted show that the applicant's capsules and the reference capsules have similar dissolution profiles.

Manufacturing process

The manufacturing process consists of mixing and encapsulation steps. An adequate flow diagram and a narrative description have been provided. The capsules are standard products, and the manufacturing process is also standard. Process validation data on the product have been presented for 3 production-scale batches in accordance with the relevant European guidelines.

Excipients

All excipients comply with their Ph.Eur. specifications. This is agreed.

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, humidity, identification, uniformity of mass, disintegration, dissolution, uniformity of content, assay, related substances, microbiological purity, blister tightness and packaging control. The analytical methods are valid. Batch analysis has been performed on twelve full-scale batches. The batch analysis results show that the finished product meets the proposed specifications.

Stability tests on the finished product

The conditions used in the stability studies are in line with the ICH stability guideline. The capsules were tested under accelerated conditions (40°C/75%RH, 6 months) and under long-term conditions (25°C/60%RH, 18-36 months). The stability control tests and the shelf-life specifications for the drug product are acceptable. Based on the submitted data, the proposed shelf-life of 3 years could be granted, with no specific storage temperature. The first three commercial batches of each strength will be enrolled in stability testing.

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 for lactose and gelatin. The magnesium stearate used is of vegetable origin.

II.2 Non clinical aspects

These products are generic formulations of Diflucan capsules, 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 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Fluconazole "Novopharm" 200 mg capsules (Novopharm Ltd, UK) is compared with the pharmacokinetic profile of the reference product Diflucan 200 mg capsules (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.

Design

A single centre, open-label, single-dose, randomised, two-way cross-over bioequivalence study was carried out under fasted conditions in 28 healthy subjects (25 male/3 female), aged 19-50 years. Each subject received a single dose (200 mg) of one of the 2 fluconazole formulations. The capsule was administered with 200 ml water after a 10 hour fasting period. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120 and 168 hours after administration of the products.

Fluconazole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fluconazole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

All subjects completed the study. According to protocol, samples from the first 24 volunteers were included in the pharmacokinetic and statistical analysis.

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

Treatment N=24	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	181.6 \pm 33.4	190.6 \pm 40.1	4.2 \pm 0.9	1.0 (0.33-6.0)	35.5 \pm 7.3
Reference	177.2 \pm 31.5	185.8 \pm 36.0	3.6 \pm 0.6	4.0 (1.0-8.0)	36.2 \pm 7.0
*Ratio (90% CI)	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.16 (1.10-1.22)	-	-
CV (%)	5.5	5.7	10.6	-	-
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 fluconazole under fasted conditions, it can be concluded that Fluconazole "Novopharm" 200 mg and Diflucan 200 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to different strengths

The 50 mg, 100 mg and 150 mg capsules are dose-proportional with the 200 mg capsule. Therefore, no bioequivalence has to be carried out with these formulations, as the results obtained for the 200 mg capsule can be extrapolated to the 50, 100 and 150 mg capsules.

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

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, 100% of the questions were successfully located and the information was very easily or easily understood by the participants. No amendments were recommended for the second test round.

The second test was also performed with 10 participants. The percentage of questions that were successfully located and understood was 98.2%. The participants experienced some difficulty in understanding question 11 "Are there any ingredients of Fluconazole that you need to be particularly aware of?". Based on the test results, no amendment to the leaflet was considered necessary.

The readability of the package leaflet has been sufficiently demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules have a proven chemical-pharmaceutical quality and are generic forms of Diflucan 50, 100, 150 and 200 mg capsules. Diflucan 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules were 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 Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 8 April 2008.

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 April 2008 to March 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 8 April 2013.

The following post-approval commitment has 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
Change in the name of the medicinal product in Italy.	NL/H/1017/001-004/IB/001	IB	12-6-2008	14-7-2008	Approval	N
Repeat use procedure with CZ, EE, FI, HU, IS, LT, LV, SK.	NL/H/1017/001-004/E/001	E	19-6-2009	21-9-2008	Approval	Y, Annex I
Withdrawal of Marketing Authorisation in Hungary.	--	Withdrawal	--	14-10-2009	Approval	N
Introduction of an additional API supplier.	NL/H/1017/001-004/IA/002	IA	24-11-2009	8-12-2009	Approval	N

ANNEX I – Repeat use procedure (NL/H/1017/001-004/E/001)

The Repeat use procedure started on 19 June 2009. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (CZ, EE, FI, HU, IS, LT, LV, SK), on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluconazole “Novopharm” 50, 100, 150 and 200 mg capsules with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 21 September 2009.

The date for the first renewal will be: 8 April 2013.

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 September 2009 to March 2011, after which the PSUR submission cycle is 3 years.

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

- 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.
- The MAH committed to submit a type II variation within 3 months to address several SPC issues.
- The MAH committed to harmonise the SPC to the future article 30 referral for Diflucan.