LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Infusiflux 2 mg/ml Solution for Infusion

SE/H/605/01/MR

This module reflects the scientific discussion for the approval of Infusiflux 2 mg/ml solution for infusion. The procedure was finalised on 23 November 2006. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Alfred E. Tiefenbacher, Germany has applied for a marketing authorisation for Infusiflux 2 mg/ml solution for infusion claiming essential similarity to Diflucan 2 mg/ml solution for infusion marketed in Sweden by Pfizer. The product contains fluconazole as active substance and is indicated for the treatment of mycoses caused by Candida, Cryptococci, and other related yeasts, in particular:

- Mucosal candida infections including oropharyngeal, eosophageal, mucocutaneous and non-invasive bronchopulmonial candidiasis and candiduria in patients with decreased immunological defence.
- Systemic candida infections, including candidemia in non-neutropenic patients.
- Prophylaxis against deep candida- infections (especially *Candida albicans*) in connection with bone marrow transplantation.
- Acute cryptococcal meningitis in adults, including patients with AIDS, transplanted patients or patients with other causes of immunosuppresion.
- Maintenance treatment to prevent recurrence of cryptococcal meningitis in patients with AIDS.

Infusiflux 2 mg/ml solution for infusion was first nationally approved in Sweden as of October 2005. A mutual recognition procedure with Sweden acting as reference member state was started in March 2006 in which five concerned member states were asked to mutually recognise and approve the product. By day 90 of the procedure, one of the concerned member states could not agree with the dosage regimen as stated in the Summary of Product Characteristics for the treatment of systemic candida infections. This triggered a CMD(h) referral procedure since potential serious risk to public health concern was raised.

Following the CMD(h) referral, agreement was reached based on the following posology: "The dose in candidaemia and other invasive Candida infections is 400-800 mg on the first day and 200-400 mg daily thereafter. The dose depends on the type and severity of the infection. In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response".

II. QUALITY ASPECTS

II.1 Introduction

Infusiflux 2 mg/ml solution for infusion is presented as a sterile solution in glass bottles. The excipients are sodium chloride and water for injections. Hydrochloric acid is used for pH adjustment.

II.2 Drug Substance

The drug substance, fluconazole is a white or almost white powder, slightly soluble in water, freely soluble in methanol, soluble in acetone.
The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

II.3 Medicinal Product

Infusiflux 2 mg/ml solution for infusion is formulated using excipients described in the current Ph Eur. The product is terminally sterilised in an autoclave.
Compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been demonstrated.
The product development has taken into consideration the physico-chemical characteristics of the active substance. The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

This product has been shown to be essentially similar to Diflucan 2 mg/ml solution for infusion. There are no new preclinical data submitted with the present application that changes the benefit/risk assessment compared with the originator. In a CPMP referral regarding capsules, text in sections 4.3 and 4.6 were changed and these texts have also been implemented in the SPC for the 2 mg/ml solution.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The product is to be administered as an aqueous intravenous solution and no difference in absorption rate or bioavailability between the two products is expected as Infusiflux 2 mg/ml and the reference product Diflucan 2 mg/ml are pharmaceutically equivalent.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar to Diflucan 2 mg/ml solution for infusion, a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Infusiflux 2 mg/ml solution for infusion is recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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