Public Assessment Report

Scientific discussion

Fluoxetine Amdipharm 60 mg, hard capsules

(fluoxetine hydrochloride)

NL/H/3535/005/DC

Date: 10 April 2018

This module reflects the scientific discussion for the approval of Fluoxetine Amdipharm 60 mg, hard capsules. The procedure was finalised on 28 November 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
List of abbreviations

ASMF     Active Substance Master File
CEP      Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP     Committee for Medicinal Products for Human Use
CMD(h)   Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS      Concerned Member State
EDMF     European Drug Master File
EDQM     European Directorate for the Quality of Medicines
EEA      European Economic Area
ERA      Environmental Risk Assessment
ICH      International Conference of Harmonisation
MAH      Marketing Authorisation Holder
Ph.Eur.  European Pharmacopoeia
PL       Package Leaflet
RH       Relative Humidity
RMP      Risk Management Plan
SmPC     Summary of Product Characteristics
TSE      Transmissible Spongiform Encephalopathy
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fluoxetine Amdipharm 60 mg, hard capsules, from Amdipharm Limited.

The product is indicated in:

Adults:
- Major depressive episodes
- Obsessive-compulsive disorder
- Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity

Children and adolescents aged 8 years and above
- Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Prozac 20 mg hard capsules which has been registered in the United Kingdom by Eli Lilly since 25 November 1988.

The concerned member states (CMS) involved in this procedure were Belgium, France, Luxembourg and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as the 60 mg strength of the product is cross-referred to the 20 mg strength of the reference product Prozac.

II. QUALITY ASPECTS

II.1 Introduction

Fluoxetine is a hard gelatin capsule with an off white opaque body marked ‘F 60’ and a green opaque cap marked ‘F 60’ containing white to off powder. Each hard capsule contains 60 mg fluoxetine as fluoxetine hydrochloride.

The hard capsules are packed in Alu-PVC blisters.

The excipients are:
- Capsule content – pregelatinised starch (maize starch) and pregelatinised starch 1500 LM (maize starch)
- Capsule shell – yellow iron oxide (E 172), patent blue V (E131), titanium dioxide (E171) and gelatin.
- Edible printing ink – shellac (E904), black iron oxide (E172), propylene glycol (E1520) and may contain potassium hydroxide (E525).

II.2 Drug Substance

The active substance is fluoxetine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder and sparingly soluble in water, freely soluble in methanol and sparingly soluble in methylene chloride. One polymorphic form is consistently produced which has been declared not to change upon storage. The substance is provided as racemic mixture of the S- and R-enantiomer.

The CEP procedure is used for the active substance. Under the 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, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

**Manufacturing process**
A CEP has been submitted; therefore no details on the manufacturing process have been included.

**Quality control of drug substance**
The active substance specification is considered adequate to control the quality and is in line with the Ph.Eur. and CEP, with additional requirements for in-house related substance impurity, residual solvents, density and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for one full batch.

**Stability of drug substance**
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

### II.3 Medicinal Product

**Pharmaceutical development**
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are appropriate. Microbiological purity and container closure system development has been adequately discussed.

The 60 mg strength has been used in the bioequivalence study against three capsules of the reference product Prozac 20 mg. The formulation of the biobatch was as per commercial formulation and the process was as per commercial manufacturing process. Comparative dissolution profiles of the 60 mg test product and 3 x 20 mg reference product in three media have been provided. Similarity has been shown. Overall, the development of the 60 mg strength is considered acceptable.

**Manufacturing process**
The manufacturing process has been validated according to relevant European guidelines and consists of sifting, mixing, blending of the common blend, followed by filling into the empty gelatin capsules. The process has been adequately described and in-process controls are adequate. Process validation data on the product have been presented for three full batches in accordance with the relevant European guidelines.

**Control of excipients**
The excipients comply with the Ph.Eur., United States pharmacopoeia or European Community. These specifications are acceptable.

**Quality 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, identity of active and colourant, average fill mass, average filled capsules, uniformity of fill mass, disintegration time, dissolution, assay, degradation products, uniformity of dosage units, microbial limits and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements/limits are identical except for maximum single unknown impurities which are higher at shelf-life. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

**Stability of drug product**
Stability data on the product have been provided on three full scaled batches stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are not fully according to the ICH stability guideline. However, no objections were made since the conditions at intermediate (75% RH instead of 65% RH) were more harsh. The batches were stored in the proposed packaging. Some fluctuations were observed for loss on drying,
disintegration and dissolution. However, no out of specification results are obtained. The results of the photostability studies show no degradation. The product is therefore considered to be stable with regard to light. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions regarding temperature or light need to be included.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The excipients gelatin is of animal origin. TSE/BSE free certificate for all the excipients used have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fluoxetine Amdipharm 60 mg, hard capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fluoxetine Amdipharm 60 mg, hard capsules is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Prozac 20 mg hard capsules which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fluoxetine hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of one capsule of the test product Fluoxetine Amdipharm 60 mg, hard capsules (Amdipharm Limited, Ireland), is compared with the pharmacokinetic profile of three capsules of the reference product Prozac 20 mg hard capsules (Eli Lilly, UK).

The choice of the reference product in the bioequivalence studies is justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.
Bioequivalence study

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-44 years. Each subject received a dose (60 mg or 3 x 20 mg) of one of the 2 fluoxetine formulations. The capsule was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 45 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.3, 7.7, 8.0, 8.3, 8.7, 9.0, 10.0, 11.0, 12.0, 24.0, 36.0, 48.0 and 72.0 after administration of the products.

The design of the study is acceptable. As fluoxetine can be taken regardless of food, a study under fasting conditions is acceptable. The half-life of fluoxetine is up to 6 days. Therefore plasma sampling until 72 hours after dosing is allowed and a wash-out period of 45 days should be sufficient.

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
Three subjects were withdrawn from the study on medical grounds. One subject due to a protocol violation (positive alcohol test) and one subject withdrew on his own accord. Therefore, 27 subjects completed the study and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-72h}$ ng.h/ml</th>
<th>C$_{max}$ ng/ml</th>
<th>$t_{max}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2204 ± 629</td>
<td>54.0 ± 10.7</td>
<td>7.7 (6.0–9.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>2152 ± 661</td>
<td>53.1 ± 13.7</td>
<td>7.7 (5.0–9.0)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.03 0.98 – 1.08</td>
<td>1.03 0.98 – 1.08</td>
<td>--</td>
</tr>
</tbody>
</table>

*ln-transformed values

Conclusion on the bioequivalence study:
The 90% confidence intervals calculated for AUC$_{0-72h}$ and C$_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study fluoxetine 60 mg, hard capsules is considered bioequivalent with (three capsules) of Prozac 20 mg hard 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluoxetine Amdipharm 60 mg, hard capsules

- Summary table of safety concerns as approved in RMP
| Important identified risks                                                                 | - Suicide/suicidal thoughts or clinical worsening of the disease |
|                                                                                         | - QT prolongation                                                |
|                                                                                         | - Activation of mania                                             |
|                                                                                         | - Haemorrhage                                                    |
| Important potential risks                                                               | - Use in pregnancy and lactation                                 |
|                                                                                         | - Effect on fertility                                             |
|                                                                                         | - Medication errors leading to overdose                          |
| Missing information                                                                      | None                                                             |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Prozac 20 mg hard capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

### V. USER CONSULTATION

The package leaflet (PL) 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. Following a pilot test with 2 participants, two rounds of testing were carried out both including 10 participants. All participants were able to trace the information for the questions and showed they understood the information by answering the questions correctly. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

### VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fluoxetine Amdipharm 60 mg, hard capsules has a proven chemical-pharmaceutical quality and is a hybrid form of Prozac 20 mg hard capsules. Prozac 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 Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluoxetine Amdipharm 60 mg, hard capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 November 2016.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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