CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fluanxol 0.5 mg, 1 mg and 5 mg, film-coated tablets Lundbeck B.V., the Netherlands

flupentixol (as dihydrochloride)

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 108182-108184

13 March 2014

Pharmacotherapeutic group:	neuroleptics (antipsychotics)
ATC code:	N05AF01
Route of administration:	oral
Therapeutic indication:	psychosis and mania
Prescription status:	prescription only
Date of authorisation in NL:	6 August 2013
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Fluanxol 0.5 mg, 1 mg and 5 mg, film-coated tablets from Lundbeck B.V. The date of authorisation was on 6 August 2013 in the Netherlands.

The product is indicated for treatment of psychosis and mania.

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

Flupentixol is a neuroleptic of the thioxanthene group. The antipsychotic effect of neuroleptics is related to their dopamine receptor blocking effect. *In vitro* and *in vivo* flupentixol has high affinity for both dopamine D1 and D2 receptors. It has only slight antihistaminergic properties and no α2-adrenoceptor blocking activity.

This national procedure concerns a line extension to Fluanxol 0.5 mg, 1 mg and 5 mg coated tablets (NL License RVG 05376, 05377, 05992), which were registered in the Netherlands by Lundbeck B.V. in 1969 (0.5 mg/1 mg) and 1970 (5 mg). These tablets are sugar-coated. With this application, the MAH introduces a film-coated tablet with a reformulated tablet core.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data.. Reference is made to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Fluanxol authorisations. Authorisations for line extensions are therefore linked to the 'original' authorised medicinal product.
The MAH provided the results of a bioequivalence study between the 'old' and 'new' formulation when administered as a single oral dose of 0.5, 1, 3 or 5 mg. Assessment of the results is discussed in section II.3 'Clinical aspects'.

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 line extension.

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 flupentixol HCL, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). No details on the manufacturing process have been included.

Quality control of drug substance
The control of the drug substance is in accordance with the Ph.Eur. with additional specifications for water content, residual solvents and sum of water and residual solvents.
The methods are conform the Ph.Eur. with some small adaptations. The analytical procedures for the deviating methods as well as the methods for water content and residual solvents are described. The corresponding validation reports were presented. Batch analyses data for 3 commercial-scale batches are submitted, showing satisfactory results.

Stability of drug substance
No stability data have been submitted, but the MAH provided a statement that the drug substance fulfils the pharmacopoeial requirements when used. This is acceptable.

** 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
Fluanxol 0.5 mg is a round, biconvex, yellow film-coated tablet marked FD.
Fluanxol 1 mg is an oval, biconvex, yellow film-coated tablet marked FF.
Fluanxol 5 mg is an oval, biconvex, ochre film-coated tablet marked FK.

The film-coated tablets are packed in Al/UPVC/PE/PVdC blisters (1 mg) or HDPE tablet containers (all strengths).

The excipients are:
Tablet core - betadex, lactose monohydrate, maize starch, hydroxypropyl cellulose, microcrystalline cellulose, croscarmellose sodium, talc, hydrogenated vegetable oil, magnesium stearate
Opadry coating mixture - polyvinyl alcohol partially hydrolysed, macrogol/PEG 3350, talc, titanium dioxide E171, iron oxide yellow E172, iron oxide red E172 (5 mg only), sunset yellow FCF (E110) (5 mg only), macrogol/PEG 6000.

The different strengths are not dose proportional, but have the same qualitative composition with respect to the core tablets only.

Pharmaceutical development
The development of the product has been described, the choice, amount and functions of the excipients are justified. Due to stability reasons it is not possible simply to film-coat the existing tablet core intended for sugar coating. This is because the sugar coating on the present coated tablets gives a very efficient protection to outer conditions that cannot be obtained by a film-coating layer. Therefore it was necessary to reformulate the Flupentixol tablet cores. No comparative dissolution data have been presented. As no biowaiver has been applied for any of the strengths and bioequivalence has been shown for each

strength, there is no objection. No comparative in-vitro dissolution data is deemed necessary. The dissolution limit of NLT 75% (Q) after 30 minutes can be accepted on the basis of the batch analysis and stability data available and supported by the specification of the sugar-coated tablet. Overall, the pharmaceutical development has been described in sufficient detail.

Manufacturing process
A flow-chart and description of the wet granulation manufacturing process have been provided, including all materials and in-process controls and mixing times and speeds. The manufacturing process has been adequately validated according to relevant European guidelines on three batches of the maximum batch size of each strength.

Control of excipients
Except for the hydrogenated vegetable oil, which is tested per BP, and the Opadry coating mixtures, tested per in-house specifications, all excipients are in line with their Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, uniformity of dosage units, dissolution, assay, related substances and microbiological purity. Except for the related substances, the release and shelf-life limits are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two full-scale batches of each strength, packed in PVC/PE/PVDC-Al blisters and HDPE containers stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No significant trends or changes were observed from the stability data. Photostability testing showed that the product is not sensitive to light. Based on the provided stability data, the proposed shelf-life of 24 months is acceptable without special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is derived from milk of a grade used for human consumption and is in compliance with current European TSE legislation. The magnesium stearate used is of vegetable origin, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a line extension to Fluanxol 0.5 mg, 1 mg and 5 mg coated tablets, which are available on the European market. No new preclinical data have been submitted. Therefore the application has not undergone additional preclinical assessment, which is acceptable for this type of application.
A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

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 flupentixol 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

Flupentixol is a well-known active substance with established efficacy and tolerability. In this application, the MAH chose to reformulate the tablets to contain a film-coat rather than a sugar-coat. An additional presentation is herewith introduced.

For this line extension, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the new products Fluanxol 0.5, 1, 3, and 5 mg film-coated tablets is compared with the pharmacokinetic profile of the existing formulation Fluanxol 0.5, 1, 3, and 5 mg coated tablet. Both products belong to Lundbeck B.V. The 3 mg strength is not on the market in the Netherlands and is not applied for. Therefore, the bioequivalence results obtained with this strength are not discussed below.

The choice of the reference product
The Fluanxol coated tablets used in the bioequivalence study have the same composition as the products on the Dutch market.
The formula and preparation of the film-coated tablets is identical to the formula proposed for marketing.

Design
A single-centre, randomised, single-dose, open-label, crossover, bioequivalence study was carried out under fasted conditions in 64 healthy male and female subjects. In the study subject were included in 4 cohorts of 16 subjects each. In these Cohorts, the subjects received two single oral doses of 0.5, 1, 3, and 5 mg flupentixol, respectively. Equal numbers of men and women were included in each cohort (8 men and 8 women), except for Cohort 1 which was comprised of 9 men and 7 women. The tablets were given with 180 mL of water, after an overnight fast (approximately 8 hours). Water was not allowed for 2 hours pre-dose until 2 hours post-dose, food was allowed from 4 hours post-dose, after the 4-hour blood sampling and safety assessments were performed. Each dose administration was separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 120 hours after administration of the products.

The design of the study is acceptable. The chosen study population is appropriate.

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 of the 64 subjects completed the study in accordance with the protocol, with the exception of 1 subject from Cohort 4. This subject (a man) withdrew his consent on day 1 of period 1 after receiving the 5 mg flupentixol sugar-coated tablet. The remaining subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of 0.5 mg flupentixol under fasted conditions.

Treatment N=16	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Film-coated tablet	4.53	5.99	0.08	12 (8-24)	54.4
Sugar-coated tablet	4.90	6.35	0.09	12 (6-24)	53.4
***Ratio (90% CI)**	0.95 (0.88-1.04)	0.99 (0.90-1.10)	0.98 (0.89-1.08)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of 1 mg flupentixol under fasted conditions.

Treatment N=16	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Film-coated tablet	10.1	13.1	0.18	12 (5-24)	56.2
Sugar-coated tablet	10.2	13.1	0.18	12 (5-16)	52.5
***Ratio (90% CI)**	0.98 (0.90-1.07)	1.00 (0.93-1.07)	1.00 (0.90-1.11)	**--**	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of 5 mg flupentixol under fasted conditions.

Treatment N=15	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Film-coated tablet	51.7	59.5	1.41	5 (5-8)	40.6
Sugar-coated tablet	45.0	53.3	1.23	5 (5-12)	44.1
***Ratio (90% CI)**	1.12 (1.04-1.21)	1.10 (1.01-1.19)	1.13 (1.03-1.24)	**--**	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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*

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 flupentixol under fasted conditions, it can be concluded that the Fluanxol film-coated and sugar-coated tablets with a strength of 0.5, 1, and 5 mg respectively are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
A total of 53 adverse events (AEs) were reported by 31 of the 64 subjects who participated in the study. The most common AEs were headache (10 subjects), fatigue (7 subjects), dizziness (4 subjects), back pain (4 subjects) and somnolence (2 subjects).
None of the subjects withdrew due to an adverse event. A similar number of adverse events were reported following administration of both the film- and sugar-coated tablets.

Fluanxol may be taken without food. From the literature it is known that food does not interact with the absorption of flupentixol. 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.

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
The MAH submitted a statement on the absence of a Risk Management Plan, and indicated that this application concerns a line extension of an active ingredient that has been in use for many years, and has a well-established safety profile. The line extension consists of a change from sugar-coated to film-coated tablets. This change in formulation does not involve any changes to the safety of flupentixol. As the safety profile of the drug is well-established, the Board agreed that a Risk Minimisation Plan is not considered necessary. 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

SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for Fluanxol coated tablets.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead a bridging report was provided in which reference is made to the English Fluanxol core PL. Based on the comparison, no issues with regard to understandability and readability are expected. Patient-friendly terms are used as much as possible. The Board considers that additional readability is not required.