LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Oxytia Depot
(oxycodone hydrochloride)

Abtard is the brand name in the UK and Oxytia is the brand name in Sweden

SE/H/1380/01-08/DC

This module reflects the scientific discussion for the approval of Oxytia Depot. The procedure was finalised at 2014-03-19. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Oxytia Depot, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, prolonged release tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, DB Ashbourne Ltd applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and UK as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Oxycontin, 5 mg, prolonged release tablets, authorised in DK since 1996, with Norpharma A/S as marketing authorisation holder.
The reference product used in the bioequivalence study is Oxycontin, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, prolonged release tablets, from DK with Norpharma A/S as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Oxytia Depot is presented in the form of prolonged release tablets containing 9, 13.5, 18, 27, 36, 54 and 72 mg of oxycodone hydrochloride which corresponds to 5, 10, 15, 20, 30, 40, 60 and 80 mg of oxycodone. The excipients are lactose monohydrate, hypromellose, povidone, stearic acid, magnesium stearate, colloidal anhydrous silica. The excipients in the tablet coating differs between the strengths as follows: *5 mg*:polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, blue Indigo Carmine Aluminium Lake (E132) and iron oxide, yellow (E172). *10 mg:* titanium dioxide (E171), hypromellose, macrogol, polysorbate 80. *15 mg*: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide, black (E172), iron oxide, yellow (E172). *20 mg*: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide, red (E172). *30 mg*: polyvinyl alcohol, macrogol, talc, iron oxide, red (E172), iron oxide, black (E172), blue Indigo Carmine Aluminium Lake (E132). *40 mg:* polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide, yellow (E172). *60 mg:* polyvinyl alcohol, macrogol, talc, iron oxide, red (E172), carmine (E120), iron oxide, black (E172). *80 mg*: polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), blue Indigo Carmine Aluminium Lake (E132), iron oxide, yellow (E172).

The tablets are packed in blister packs of PVC/Al or PVC/PVdC/Al/PET/paper (child-resistant) and HDPE tablet containers with LDPE caps.

II.2 Drug Substance

Oxycodone hydrochloride has a monograph in the Ph Eur.

Oxycodone hydrochloride is a white or almost white crystalline powder which is freely soluble in water. The structure of oxycodone hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Oxytia Depot is formulated using excipients described in the current Ph Eur, except for iron oxide and blue Indigo Carmine Aluminium Lake (E132) which are controlled according to acceptable JP and in house specifications, respectively. All raw materials used in the product are of vegetable origin except lactose which has been demonstrated to comply 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).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as hygroscopic properties.

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 data presented support the shelf life claimed in the SPC, with no special storage precautions for storage in HDPE container and when stored below 25°C for blister.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application the applicant has submitted twelve bioequivalence studies comparing oxycodone prolonged release tablet with Oxycontin prolonged release tablet. A single dose bioequivalence study under fasting condition was performed on all applied strength (i.e. 5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg and 80mg). The applicant also performed a single dose bioequivalence study under fed condition on the 80 mg strength, a steady state bioequivalence study under fasting condition on the 20mg strength as well as the 80 mg

strength and a combined single dose study under fed condition and a steady state study under fasting condition performed at the 5 mg strength. The submitted studies are described below:

Eight single dose, two-way, cross-over studies were performed, where blood samples were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of oxycodone were determined with a validated LC-MS/MS method. For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A combined single dose study under fed condition and a steady state study under fasting condition were performed at the 5 mg strength as a two-way cross over study. Blood samples were collected pre-dose and up to 24 hours post-dose day 1 as well as pre-dose and up to 12 hours post-dose day 5. Plasma concentrations of oxycodone were determined with a validated LC/MS/MS method. The 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the single dose study as well as for $AUC_{0-\tau}$, C_{max} and C_{min} for the multiple dose study.

A multiple dose, two-way crossover study under fasting condition was performed at the 20 mg strength. Blood samples were collected pre-dose day 1, 2, 3 and 4. On Day 5, blood samples were collected pre-dose and up to 12 hours post dose. Plasma concentrations of oxycodone were determined with a validated LC/MS/MS method. For $AUC_{0-\tau}$, C_{max} and C_{min} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A single dose, two-way crossover study under fed condition was performed at the 80 mg strength where blood samples were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of oxycodone were determined with a validated LC-MS/MS method. For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

One multiple dose, two-way crossover study under fasting condition was performed at the 80 mg strength. Blood samples were collected pre-dose and up to 12 hours post dose on day 4 and day 8. Plasma concentrations of oxycodone were determined with a validated LC-MS/MS method. For $AUC_{0-\tau}$, C_{max} and C_{min} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The applied product is a single unit formulation. If the Note for guidance on modified release oral and transdermal dosage forms (CPMP/EWP/280/96) should be strictly followed a complete study package (i.e. a single dose bioequivalence study under fasting condition, a single dose bioequivalence study under fed condition and a multiple dose bioequivalence study under fasting condition) is required on each strength since the different applied strengths do not fulfil the requirement of pharmaceutical proportionality. However in this case a bracketing approach might be acceptable. A single dose bioequivalence study under fasting condition was performed on all strengths and a complete study package was performed at the lowest strength and the highest strength. This is considered sufficient since the lowest and the highest strength is considered the worst case formulations i.e. the highest and the lowest strength of the applied strengths and the lowest and the highest strength also represent the formulations differing most in release controlling polymer content. Thus, the submitted study package is considered sufficient and no additional studies are considered necessary.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to 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

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Oxikodon Actavis (Reltebon) capsules hard, SE/H/1226/01-03/DC. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Oxytia Depot, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, prolonged release tablets, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Oxytia Depot, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg, prolonged release tablets was successfully finalised on 2014-03-19.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se