CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Naltrexon Hydrochloride Accord 50 mg film-coated tablets
Accord Healthcare Ltd, United Kingdom

naltrexone (as hydrochloride)

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/1151/001/DC
Registration number in the Netherlands: RVG 102900

21 June 2010

Pharmacotherapeutic group:	drugs used in addictive disorders, drugs used in alcohol dependence
ATC code:	N07BB04
Route of administration:	oral
Therapeutic indication:	additional therapy within a comprehensive treatment program including psychological guidance for detoxified patients who have been opioid-dependent & alcohol dependent to support abstinence.
Prescription status:	prescription only
Date of authorisation in NL:	6 May 2010
Concerned Member States:	Decentralised procedure with BE, DE, DK, EE, ES, FI, IE, IT, LT, LV, NO, PL, PT, UK
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 Naltrexon Hydrochloride Accord 50 mg film-coated tablets, from Accord Healthcare Ltd. The date of authorisation was on 6 May 2010 in the Netherlands.

The product is indicated for use as an additional therapy within a comprehensive treatment program including psychological guidance for detoxified patients who have been opioid-dependent & alcohol dependence to support abstinence.

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

Naltrexone is a specific opioid antagonist with only minimal agonistic activity. It acts by stereospecific competition with receptors which are mainly located in the central and peripheral nervous system. Naltrexone competitively binds to these receptors and blocks the access for exogenously administered opioids. Naltrexone treatment does not lead to physical or mental dependence. No tolerance for the opioid antagonising effect is seen.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nalorex 50 mg film-coated tablets (NL License RVG 11511) which was first registered in the Netherlands by Bristol-Myers Squibb B.V. on 22 November 1988. In addition, reference is made to Nalorex authorisations in the individual member states (reference product). The reference product is also registered in several member states under the brand name Revia, specifically indicated for treatment of alcohol dependence. In some other CMSs (BE, ES, IT, LT, LV and PL) no reference product is marketed and the MAH refers to the Dutch Nalorex product as a European 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 Nalorex 50 mg film-coated tablets, 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 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 naltrexone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is freely soluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride. The active substance is very hygroscopic. Naltrexone hydrochloride has four chiral centra. No polymorphism is observed.

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/EMEA 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.>

Manufacturing process
The manufacturing process consists of 3 steps. Control of materials as well as validation of the manufacturing process and the manufacturing process development has been sufficiently elucidated.

Quality control of drug substance
The drug substance is controlled in accordance with the current Ph.Eur. monograph. This is considered to be acceptable. The analytical methods are also in compliance with Ph.Eur. Possible genotoxic impurities are adequately controlled; acceptable limits have been set. Batch analysis has been performed on two full-scale batches, demonstrating compliance with the specification.

Stability of drug substance
The stability data have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and at 30°/60% RH (60 months) and at 40°C/75% RH (6 months). The drug substance was adequately stored. No out of specification values were observed. The claimed a retest period of 1 year could therefore be granted.

** 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
Naltrexon Hydrochloride Accord 50 mg is a yellow colored, oval, biconvex, film-coated tablet with a breakline on one side and plain on the other side.
The tablet can be divided into equal halves.

The film-coated tablets are packed in white opaque PVC/PE/Aclar – Alu blister and Alu-Alu blister packs.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal anhydrous silica , magnesium stearate.

Film-coating - hypromellose (E464), macrogol 400, polysorbate 80 (E 433), iron oxide yellow (E172), iron oxide red (E172), titanium dioxide (E171).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The UK reference product used in the bioequivalence study is acceptable. The manufacturing process of the test batch used in the bioequivalence study and clinical trials is the same as the manufacturing process of the product to be marketed.
Other development studies performed were:

- Influence of manufacturing process on assay.
- Influence of hardness and excipients on dissolution.
- Optimisation of blending time, lubricant concentration and disintegrant concentration.

As the tablets can be divided into equal halves, subdivision of tablets is included in the specifications and controlled in accordance with the Ph.Eur. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation followed by compression and is considered to be a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale and one pilot-scale batch. The product is manufactured using conventional manufacturing techniques. Additional process validation on commercial-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight, water, identification, dissolution, uniformity of dosage units, related substance, assay, microbial limit test and subdivision of tablets. The release and shelf-life limits for related substances are generally in line with the Ph.Eur. limits. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two full-scale and one pilot-scale batch demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two full-scale and one pilot-scale batch. The batches were stored at 25°C/60%RH (24 months) and 40°C.75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu-Alu blisters and white opaque PVC/PE/Aclar-Alu blisters. Some slight upward trends were observed under both long term and accelerated conditions, but all values stayed within the specifications. The proposed shelf-life of 24 months packaged in Alu-Alu blister or white opaque PVC/PE/Aclar-Alu blisters without special storage conditions was therefore granted.
The MAH committed to place the first three production batches on long-term stability throughout the proposed shelf life and on accelerated studies for 6 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is prepared without the use of other ruminant materials than milk and calf rennet. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption. The magnesium stearate used is not derived from and does not contain raw materials of animal origin.

II.2 Non clinical aspects

This product is a generic formulation of Nalorex 50 mg film-coated tablets, which is 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 naltrexone 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

Naltrexone 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 Naltrexon Hydrochloride Accord 50 mg (Accord Healthcare Ltd) is compared with the pharmacokinetic profile of the reference product Nalorex 50 mg tablets (Bristol-Myers Squibb, Spain).

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 open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study was carried out under fasted conditions in 40 (+ 2 alternate) healthy male subjects, aged 23.5 ± 3.58 years. Each subject received a single dose (50 mg) of one of the 2 naltrexone formulations. The tablet was orally administered with 240 ml water in sitting posture after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after administration of the products.

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
Thirty-eight subjects completed the clinical phase of the trial. One subject was withdrawn from the trial due to emesis and his plasma samples were analyzed for the safety evaluation only. Another subject withdrew his consent before Period II. The plasma samples obtained from the 38 subjects who completed the study entirely were analysed to obtain concentrations for naltrexone and its metabolite, 6-ß-naltrexol.

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	35.15 ± 15.75	36.46 ± 16.04	10.99 ± 4.86	1.0 (0.5-3.0)	-
Reference	36.98 ± 21.02	38.23 ± 21.64	10.87 ± 5.12	1.0 (0.5-2.0)	-
***Ratio (90%**	0.97 (0.92-1.02)	0.97 (0.93-1.02)	1.01 (0.92-1.12)	-	-

CI)					
CV (%)	18.8	18.6	24.6	-	-
$AUC_{0-\infty}$ 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 ± SD, t_{max} (median, range)) of 6-ß-naltrexol under fasted conditions.

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	785.22 ± 174.81	799.508 ± 177.95	93.51 ± 26.34	1.0 (0.5-3.0)	-
Reference	781.66 ± 173.94	796.97 ± 178.69	88.71 ± 24.31	1.0 (0.5-2.0)	-
***Ratio (90% CI)**	1.01 (0.98-1.03)	1.00 (0.98-1.03)	1.05 (0.96-1.16)	-	-
CV (%)	5.8	5.9	23.1	-	-
$AUC_{0-\infty}$ 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 naltrexone under fasted conditions, supported by metabolite data, it can be concluded that Naltrexon Hydrochloride Accord 50 mg and Nalorex 50 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Naltrexone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of naltrexone. 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

Naltrexone was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of naltrexone 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 was adapted in line with the current SPCs of IE/H/153/001/MR and IE/H/154/001/MR, concerning other naltrexone generics. Initially, the application involved only the indication for use in opioid-dependent patients. In several member states naltrexone hydrochloride 50 mg is however also indicated for treatment of alcohol dependence. The MAH followed the advise to include this indication and related information from the SPC of Revia, since Nalorex and Revia are part of the same global marketing authorization.

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 two rounds with 10 participants each. Sex (10 male/10 female), age, education were rated and medical training was excluded. Questions on finding and understanding were asked in a randomised way on predefined key safety issues.
Overall the test has been performed well and scoring met the preset criteria. No changes between 2 rounds of testing were necessary and scoring was very high: finding of answers scored 99.3% and understanding 98.6%.
The report is clear and the conclusions are acceptable. No problems were seen with the package leaflet provided. The final PIL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Naltrexon Hydrochloride Accord 50 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Nalorex 50 mg film-coated tablets. Nalorex 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. However, one issue needs to be resolved (see below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other naltrexone containing products.

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 Naltrexon Hydrochloride Accord 50 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 February 2010. Naltrexon Hydrochloride Accord 50 mg film-coated tablets was authorised in the Netherlands on 6 May 2010.

A European harmonised birth date has been allocated (20 November 1984) and subsequently the first data lock point for naltrexone is November 2012. The first PSUR will cover the period from February 2010 to November 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 May 2013.

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

Quality - medicinal product

- The MAH committed to further validate the manufacturing process on the first 3 batches of commercial scale.
- The MAH committed to place the first three production batches on long-term stability throughout the proposed shelf life and on accelerated studies for 6 months.

Pharmacovigilance system

- The MAH committed to appoint a qualified person for Pharmacovigilance and to ensure compliance with the Belgian requirements before placing the product on Belgian market.

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