CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Aspendos 100 mg tablets
Medochemie Limited, Cyprus

modafinil

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/1816/001/DC
Registration number in the Netherlands: RVG 105888

19 January 2011

Pharmacotherapeutic group:	centrally acting sympathomimetics
ATC code:	N06BA
Route of administration:	oral
Therapeutic indication:	excessive sleepiness associated with narcolepsy with or without cataplexy
Prescription status:	prescription only
Date of authorisation in NL:	12 January 2011
Concerned Member States:	Decentralised procedure with BG, CY, CZ, RO, EL and SK
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 Aspendos 100 mg tablets, from Medochemie Limited. The date of authorisation was on 12 January 2011 in the Netherlands. The product is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Excessive sleepiness is defined as difficulty maintaining wakefulness and an increased likelihood of falling asleep in inappropriate situations.

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

Modafinil promotes wakefulness in a variety of species, including man. The precise mechanism(s) through which modafinil promotes wakefulness is unknown. In non-clinical models, modafinil has weak to negligible interactions with receptors involved in the regulation of sleep/wake states (e.g., adenosine, benzodiazepine, dopamine, GABA, histamine, melatonin, norepinephrine, orexin, and serotonin). Modafinil also does not inhibit the activities of adenylyl cyclase, catechol-O-methyltransferase, glutamic acid decarboxylase MAO-A or B, nitric oxide synthetase, phosphodiesterases II-VI, or tyrosine hydroxylase. While modafinil is not a directacting dopamine receptor agonist, *in vitro* and *in vivo* data indicate that modafinil binds to the dopamine transporter and inhibits dopamine reuptake. The wake-promoting effects of modafinil are antagonised by D1/D2 receptor antagonists suggesting that it has indirect D1/D2 receptor agonist activity.
Modafinil does not appear to be a direct α1-adrenoceptor agonist. However, modafinil binds to the norepinephrine transporter and inhibits norepinephrine uptake, but these interactions are weaker than those observed with the dopamine transporter. Although modafinil-induced wakefulness can be attenuated by the α1-adrenoceptor antagonist, prazosin, modafinil is inactive in other assay systems (e.g. vas deferens) responsive to α-adrenoceptor agonists.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Modiodal 100 mg tablets, (NL license RVG 18535) which have been registered in France by Cephalon France since 1992 (original product). In the Netherlands, Modiodal 100 mg tablets have been registered since 1997. In addition, reference is made to Modiodal authorisations in the individual member states (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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Modiodal 100 mg tablets, registered in France. 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 generic medicinal products.

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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 drug substance is Modafinil, an established drug substance described in the Ph.Eur* as well as the BP* and the USP*. The drug substance is very slightly soluble or practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96%). Its polymorph form is form I. The substance is a racemate. Modafinil shows polymorphism. Only form 1 is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance from one source. 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.

The CEP procedure is used for the active substance from another source. 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 new 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
The synthesis processes, starting materials, solvents and reagents from the ASM holder have been included in the description. The drug substance supplied by this supplier is formed in a three step process. The drug substance supplied by the other supplier is formed in a two step process. The active substance from both suppliers has been adequately characterized. No class 1 organic has been used in either of the manufacturing processes of the supplied drug substances.

Quality control of drug substance
The drug substance specifications have been established for both manufacturers as well as the MAH. They are based on the Ph.Eur. methods and in-house methods. The specifications are acceptable in view of the route of synthesis and European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches from one supplier and six batches from the other supplier on full scaled as well as pilot scaled batches.

Stability of drug substance
Supplier 1 - The active has a retest period of 5 years when stored as indicated on the CEP.
Supplier 2 - Stability data on the active substance have been provided for 7 production scaled batches. The batches were adequately stored at 25°C/60%RH (9-60 months) and at 40°C/75%RH (6 months). Results of the accelerated and long term storage conditions showed no specific up or downwards trend in any of the parameters tested. The claimed re-test period of 60 months is for the substance from this supplier is justified. The claimed storage condition (none) is justified as well.

MAH –The container closure system and storage conditions and re-test period the MAH chose to apply to the substance from the second manufacturer are acceptable, as these are similar to the conditions applied by the first supplier. The substance from the first manufacturer will be stored according to the CEP indications.
For the substances from both suppliers the MAH applied for a re-test period of 2 years, which is acceptable in view of the stability data.

** Ph.Eur., USP, and BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Aspendos 100 mg are white, round, biconvex, tablets which are packed in PVC/ Aluminium blisters.

The excipients are: lactose monohydrate, maize starch, croscarmellose sodium (E468), aluminium magnesium silicate, povidone K 90 (E1201), talc (E553b), magnesium stearate (E572).

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Comparative dissolution profiles were provided similarity between the innovator and reference product is shown. The choices of the packaging and manufacturing process are justified.

Manufacturing process
The tablets are manufactured by means of a 5 step process including preblending, wet granulation and drying, final blending, tabletting and packing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 4 batches of pilot -and production scaled size. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorization.

Container closure system
The packaging materials were chosen with reference to the commercial pack required, and the stability of the tablets under ICH accelerated, real-time testing conditions as well as photostability in which the materials were shown to provide good protection of the tablets from environmental influence (heat, moisture, light etc.). The packaging materials comply with regulations 90/128/EEC, 78/142/EEC and with European Pharmacopoeia monograph 3.1.11 Materials based on non- plasticized poly(vinyl chloride) for containers for dry dosage forms for oral administration. The specifications include description, identification and critical quality parameters as well as routine tests for all the above-mentioned materials, are given. An IR spectrum for the PVC foil is included as well as CoA's for both the foil and the PVC material. The provided information is regarded as sufficient.

Excipients
All excipients comply with their specifications of the Ph.Eur. monographs.

Quality control of drug product
The product specification includes tests for description, average weight, uniformity of dosage units (mass variation), identification by IR and HPLC, disintegration, dissolution, assay, related substances, and microbiological contamination. Release and end of shelf-life specification are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 4 pilot/production scaled batches, demonstrating compliance with the release specification. Additional batch data of commercial scale batches will be available on request of the authorities.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The product does not show antimicrobial activity and the specification and microbiological method for the microbiological burden was chosen to be according to the general monograph of Ph.Eur. 2.6.12.

Compatibility
No incompatibility between the excipients was reported in literature. Compatibility of the active ingredient with the excipients and with the immediate container was confirmed by the results of the stability studies performed.

Stability tests on the finished product
Stability data on the product have been provided for two pilot scaled batches and for two production scaled batches stored at 25°C/60%RH (18 months), 30°C/65%RH (18 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 adequately stored in. Results stayed within limits although a significant increase was seen at accelerated conditions for assay. A shelf-life of 21 months can be granted for the product stored below 30°C.
The MAH committed to continue stability studies for the pilot and production scaled batches included in the stability studies thus far.

Photostability
Photostability test showed that the drug product is stable under light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The magnesium stearate from one supplier is of bovine origin, a valid TSE CEP is provided. The other suppliers of magnesium stearate supply magnesium stearate of vegetable/plant origin. For the lactose monohydrate a statement on minimizing the risk of TSE is included.

II.2 Non clinical aspects

This product is a generic formulation of Modiodal, 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 modafinil 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

Modafinil is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Aspendos 100 mg tablets (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Modiodal 100 mg tablets (Cephalon France, France).

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 (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

A single centre, open, single-dose, randomized, two-period, two-treatment, two sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy volunteers. Nineteen subjects were non-smokers, six subjects were mild smokers (up to 9 cigarettes per day). Each subject received a single dose (100 mg) of one of the 2 modafinil formulations. The tablet was orally administered with 200 ml water after a fasting period of 11 hours. Fasting was continued for 24 hours after dosing. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 72.0 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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

Results

Five adverse events occurred in five subjects: vomiting (1 subject), headache (3 subjects) and acute rhinitis (1 subject).

The severity of the AEs was mild in four cases and moderate in one case (vomiting).
One subject was withdrawn from the study during the washout due to an adverse event (vomiting). Twenty-five subjects completed study Period 2, passed all study procedures and were employed for the bioequivalence assessment. All subjects who received at least one dose of the treatment were included in the safety analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	23913,7 ± 6701.4	25472,0 ± 7265.8	2131,3 ± 447.0	1,67 (0.50 – 6.00)	10.45 ± 2.31
Reference	23465,9 ± 6774,1	24988,5 ± 7123,2	2217,5 ± 449,5	1.33 (0.5 – 3.5)	10,78 ± 2,58
*Ratio (90% CI)	1.02 (1.00 – 1.04)	1.02 (1.00 – 1.04)	0.96 (0.91 – 1.01)	---	---
CV (%)	3.8	3.6	10.4	---	---

$AUC_{0-\infty}$ 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 (active substance) under fasted conditions, it can be concluded that Aspendos 100 mg tablets and Modiodal 100 mg tablets are bioequivalent with respect to rate and extent

of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

Modafinil was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of modafinil 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 is in line with the SPC that is agreed at the harmonisation procedure for the SPC of Modafilnil (procedure EMEA/H/A-31-1186).

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. Face to face interviews were taken. Two stages of testing were performed, each involving 10 subjects, preceded by a preliminary pilot round of testing with four subjects. The participants were questioned about the leaflet in an evaluation and problem-seeking test. The report details the demographic data of the volunteers, age, gender, social grade and education. Recruiting was performed by placing an advertisement in a local news paper.

The questionnaire for this user test contained 14 questions specific to the key safety issues of Modafinil and 3 questions general to the format of the leaflet. The questions sufficiently address the key safety messages. In addition, 3 general questions about the leaflet and its lay-out were drawn up. A satisfactory test outcome is when 9 of the 10 participants of each round are able to find the information requested within the PIL, of whom at least 8 of these 9 subjects can show that they understand it.

The original PIL has been provided in the report. No revisions were made to the PIL after the preliminary testing round with four participants and no revisions were made to the PIL after the first and second round.

In round 1 all the participants were able to find the information requested (simple and easy) and all participants showed that they understood and acted upon it (most of the participants simple and easy, one participant moderate at question 5). No corrective actions were taken to the PIL for round 2.

In round 2, all the participants were able to find the information requested (simple and easy) and all showed that they understood and acted upon it (simple and easy). (The correct answer was traced in all of 14 questions by all participants. All subjects were able to show comprehension of the information, and the PIL passed the test criteria. The contents and lay-out of the PIL are acceptable. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Aspendos 100 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Modiodal 100 mg tablets. Modiodal 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.

The SPC is in line with the SPC that is agreed at the harmonisation procedure for the SPC of Modafilnil (procedure EMEA/H/A-31-1186, finalised with a CHMP opinion on 21 July 2010). The SPC, package leaflet and labelling are in the agreed templates.

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 Aspendos 100 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 October 2010. Aspendos 100 mg tablets are authorised in the Netherlands on 12 January 2011.

A European harmonised birth date has been allocated 1 September 1994 and subsequently the granting of the marketing authorisation first data lock point for modafinil is August 2012. The first PSUR will cover the period from to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be April 2013

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

<u>Quality - medicinal product</u>
- The MAH has committed to validate the first three batches produced for the minimum and maximum batch sizes. As soon as the data will be available, the validation report will be submitted to the Authorities.
- The MAH committed to continue stability studies for the pilot and production scaled batches included in the stability studies thus far.
- The MAH has committed to place the first three commercial scale batches on stability. One batch will be added to ongoing stability program annually.

<u>SPC</u>
- The MAH committed to promptly respond to the CHMP decisions and keep the SPC and the PIL in line with the reference products once the article 31 referral has concluded by the EC.

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