CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Modafinil Orchid 100 mg and 200 mg, tablets
Orchid Europe Ltd, United Kingdom

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/1278/001-002/DC
Registration number in the Netherlands: RVG 102358, 102360

10 June 2010

Pharmacotherapeutic group:	psychostimulants, agents used for ADHD and nootropics, centrally acting sympathomimetics
ATC code:	N06BA07
Route of administration:	oral
Therapeutic indication:	symptomatic relief of excessive sleepiness associated with narcolepsy
Prescription status:	prescription only
Date of authorisation in NL:	10 May 2010
Concerned Member States:	Decentralised procedure with BE, DE, DK, ES, FI, FR, IE, IT, PL, SE, 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 Modafinil Orchid 100 mg and 200 mg, tablets from Orchid Europe Ltd. The date of authorisation was on 10 May 2010 in the Netherlands. The product is indicated for the symptomatic relief of excessive sleepiness associated with narcolepsy.

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

Modafinil is a centrally acting sympathomimetic substance. It promotes wakefulness in a variety of species, including man. The precise mechanism(s) through which modafinil promotes wakefulness is unknown. In pre-clinical models, modafinil does not appear to be a direct or indirect acting alpha$_1$-adrenoceptor or dopamine receptor agonist. The wakefulness induced by amfetamine, but not by modafinil, is antagonised by the dopamine receptor antagonist haloperidol. Equal wakefulness-promoting doses of methylphenidate and amfetamine increase neuronal activation throughout the brain, but modafinil selectively and prominently increases neuronal activation in more discrete regions of the brain, especially in the hypothalamus.

In man, modafinil restores and/or improves the level and duration of wakefulness and daytime alertness in a dose-related manner. Administration of modafinil results in electrophysiological changes indicative of increased alertness and improvements in objective measures of ability to sustain wakefulness. Modafinil opposes the impairment of cognitive, psychomotor and neurosensorial performance induced by sleep deprivation. These changes are produced without any adverse changes in behaviour and appetite.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Modiodal 100 mg tablets (NL License RVG 18535) which has been registered in the Netherlands by Cephalon France since 13 November 1997. The marketing authorisation for the 100 mg product is granted based on article 10(1) of Directive 2001/83/EC.
For the 200 mg product, the application is made according to article 10(3) of Directive 2001/83/EC, *i.e.* a hybrid application with a difference in strength. In the CMSs the applications are made according to article 10(1) of Directive 2001/83/EC and article 10(3) of Directive 2001/83/EC, depending on the innovator product registration.

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 200 mg product is compared with the pharmacokinetic profile of the reference product Provigil 200 mg, 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. These generic products can be used instead of their reference products.

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 an 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 modafinil, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder, which is very slightly soluble or practically insoluble in water, slightly soluble in ethanol and sparingly soluble in methanol. Due to the starting material and manufacturing process no isomers are possible. Polymorphism can occur; only polymorphic form I is formed.

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 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.

Manufacturing process
The preparation of Modafinil consists of a three step manufacturing process. The process has been adequately characterized and acceptable specifications have been adopted for the used solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for polymorphism, optical rotation, residual solvents and particle size. The methods and limits included in the specification are acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for four full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for four full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequatley stored. No trends or out of specification values were observed. No photostability study was conducted, given the packaging material. This is considered to be acceptable. Based on the results provided, a retest period of 24 months could be granted, with the applicable storage condition *store in the original package in order to protect from light.*

* *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
Modafinil Orchid 100 mg is a white to off white coloured capsule shaped tablet debossed with 'M' on one side and '100 MG' on the other side.
Modafinil Orchid 200 mg is a white to off white coloured capsule shaped tablet debossed with “M” on one side and “200,MG” on the other side with a breakline between 200 and MG.
The tablet can be divided into equal halves.

The different tablet strengths are dose proportional.

The tablets are packed in PVC/Aclar or Al/Al blister packs.

The excipients are: crospovidone (Type A), crospovidone (Type B), microcrystalline cellulose, pregelatinized maize starch, Povidone K-90, Povidone K-30, lactose monohydrate, colloidal anhydrous silica, talc, magnesium stearate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to manufacture a drug product which is bioequivalent to the innovator product. In order to achieve this objective, dissolution studies were carried out to develop the final product demonstrating that the dissolution profiles of the innovator product and the Modafinil tablets are comparable.
The final composition was developed by optimizing the dissolution profile through varying the amount of the different excipients in the tablets. Furthermore, the dissolution profiles of both dry and wet granulation were compared with each other. Given the results wet granulation was chosen as granulation method.
The packaging of the tablets in the clear PVC/Aclar- or opaque Alu/Alu-blisters is considered usual for tablets. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of granulation, blending, lubrication and compression steps, after which the tablets are packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four pilot-scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-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 appearance, identification, water content, average weight, uniformity of dosage units by mass variation, microbial limits, disintegration time, dissolution, assay and related substances. All limits and requirements are the same for both the release and shelf-life specification, with the exception of the related substances.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches, demonstrating compliance with the release specification. The MAH committed to provide batch analysis data on the first three production-scale batches.

Stability of drug product
Stability data on the product have been provided on four pilot-scale batches (two per strength) 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 both blister packagings. Under both conditions a slight variation in assay was observed. This was considered to be a variation in the analytical method. No other trends were observed. All values stayed within the specifications. Furthermore, a photostability study was conducted demonstrating that the drug product is photostable. Based on these results, the claimed shelf-life of 24 months without special storage conditions was granted for the tablets packed in the clear PVC/Aclar- or opaque Alu/Alu blisters.

The MAH made several commitments regarding continuation of the stability studies; these can be found on page 8 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The lactose used is derived from milk that has been retrieved from healthy animals in the same way as milk for human consumption. The magnesium stearate is of vegetable origin.

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 a bioequivalence study in which the pharmacokinetic profile of the test product Modafinil Orchid 200 mg (Orchid Europe Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Provigil 200 mg tablets (Cephalon UK Limited).

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 single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 20 healthy male subjects. Each subject received a single dose (200 mg) of one of the 2 modafinil formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 18 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 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
All 20 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 modafinil under fasted conditions.

Treatment N=20	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	109.47 ± 27.40	119.51 ± 34.24	7.45 ± 1.09	2.5 (1.0-4.0)	-
Reference	109.34 ± 26.49	119.35 ± 32.75	7.57 ± 1.23	3.0 (1.0-6.0)	-

***Ratio (90% CI)**	1.00 (0.99-1.01)	1.00 (0.99-1.02)	0.98 (0.94-1.03)	-	-
CV (%)	2.45	2.79	7.61	-	-
$AUC_{0-\infty}$ 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 modafinil under fasted conditions, it can be concluded that Modafinil Orchid 200 mg and Provigil 200 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.

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.

Extrapolation to 100 mg
The 100 mg tablets are dose proportional with the 200 mg tablets, and both strengths are manufactured through the same process. The pharmacokinetics of the active substance are linear. In addition, the dissolution profiles of both strengths are comparable. The results of the bioequivalence study performed with the 200 mg tablet therefore apply to the 100 mg tablet as well.

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
During the procedure the proposed additional indications obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and moderate to severe chronic shift work sleep disorder (SWSD), were withdrawn. For the innovator product Modiodal, an article 31 referral is currently ongoing. The MAH committed to update the SPC as soon as this referral has been finalized.

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 a pilot test with 2 participants, followed by two rounds with 10 participants each. Participants aged 18-70 years of age were recruited as potential users of Modafinil. The questionnaire consisted of 17 questions dealing with important key safety

issues, which have been identified by the MAH. Furthermore 4 questions were asked to gain information on design and layout of the PIL. The questionnaire contained both questions on technical readability and traceability as well as applicability questions, used to investigate the comprehensibility and the applicability of the information.
A satisfactory test result was defined as 90% of all participants being able to trace 90% of the information. These participants must be able to show they comprehend at least 90% of the information. In both rounds the results showed that the information to answer each question was traced 100% of the time and each participant showed that he or she understood the information by answering the questions correctly nearly 100% of the time (One person in the first round answered 1 question incorrectly, all others answered 100% of the questions correctly). Based on these results, it can be concluded that the information in the PL is easy to trace and to comprehend. No modifications to the PIL have been made in between testing rounds. Most participants mentioned that the font size of the PIL is fine for reading. Therefore, no changes have been made to the lay-out of the PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Modafinil Orchid 100 mg and 200 mg, tablets have a proven chemical-pharmaceutical quality and is a generic form of Modiodal 100 mg and 200 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, package leaflet and labelling are in the agreed templates and are in agreement with other modafinil 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 Modafinil Orchid 100 mg and 200 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 December 2009. Modafinil Orchid 100 mg and 200 mg, tablets were authorised in the Netherlands on 10 May 2010.

A European harmonised birth date has been allocated (1 September 1994) and subsequently the first data lock point for modafinil is August 2012. The first PSUR will cover the period from December 2009 to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 23 December 2014.

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

Quality - medicinal product

- The MAH committed to provide batch analysis data on the first three production-scale batches.
- The MAH committed to continue the stability studies in the subsequent stations as per protocol given.
- The MAH committed to continue stability studies for the submission batches under long-term conditions up to 36 months as per the stability schedule provided.
- The MAH committed to place the first 3 commercial batches on stability studies at accelerated conditions (at 40°C ± 2°C and 75% ± 5% RH) for a period of 6 months and long term conditions (25°C ± 2° C and 60 % ± 5 % RH) up to 36 months.
- The MAH committed to place at least one commercial batch per year on long-term stability studies (25°C ± 2° C and 60 % ± 5 %RH) in the marketed container closure system.

Product information

- The MAH committed to update the product information as soon as the article 31 referral for Modiodal has been finalized.

Pharmacovigilance system

- The MAH committed to follow the risk management plan for the innovator product, where appropriate, in case such a plan will be constituted in the article 31 referral of modafinil containing products.

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