IPAR

HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Prosentio 100 and 200 mg Tablets
MODAFINIL
PA0126/190/001-002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Prosentio 100mg and 200mg Tablets from Clonmel Healthcare Limited on 6th July 2012 for the treatment in adults 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.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. This means that Prosentio tablets contains the same qualitative and quantitative composition in active substance as the reference product, is the same pharmaceutical form as the reference product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The reference medicinal product is Provigil 100mg and 200mg tablets.

This product is licenced for sale and supply under medical prescription which cannot be renewed. It may be advertised to the healthcare professions as a prescription-only product.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.HPRA.ie

Name of the product	Prosentio 100mg and 200mg Tablets
Name(s) of the active substance(s) (INN)	MODAFINIL
Pharmacotherapeutic classification (ATC code)	N06BA07
Pharmaceutical form and strength(s)	100 mg and 200 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0126/190/001-002
Marketing Authorisation Holder	Clonmel Healthcare Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Prosentio 100mg and 200mg Tablets.

II.2 Drug substance

The active substance is modafinil an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Prosentio are white to off-white coloured, capsule shaped tablets. The 100mg tablets are debossed with 'M' on one side

and ‘100MG’ on the other side. The 200mg tablets are debossed with ‘M’ on one side and ‘200MG’ on the other side with a breakline between 200 and MG.

Each tablet contains 100mg or 200mg modafinil. The other ingredients are crospovidone, pregelatinised starch, microcrystalline cellulose, povidone, lactose monohydrate, silica, colloidal anhydrous, talc and magnesium stearate.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. and are therefore adequately controlled by the manufacturer’s specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as PVC/Aclar/Aluminium blisters or Aluminium/Aluminium blisters containing 10, 14, 15, 20, 28, 30, 56, 60, 90, 100 and 250 tablets per package. Not all pack sizes may be marketed.

Evidence has been provided that blisters complies with relevant Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored in the original package. Based on the stability data provided, this medicinal product does not require any special storage conditions.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Prosentio.

IV CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Provigil marketed by Cephalon UK Limited.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Modafinil is compared with the pharmacokinetic profile of the reference product Provigil.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Modafinil 200mg tablets were compared to the reference product Provigil 200mg tablets, Cephalon. Based on the pharmacokinetic parameters of active substance, the reference tablet Modafinil and test tablet Provigil are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 200mg tablets are dose proportional with the 100mg tablets. The pharmacokinetics of the active substance are linear in the dosage range. The results of the bioequivalence study performed with the 200mg tablets therefore apply to the other strengths.

Modafinil participates in the PSUR Worksharing project at the Heads of Medicines Agency. Modafinil is currently subject to yearly PSUR submissions, with the next data-lock point due in August 2012.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Provigil marketed by Cephalon UK Limited.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Modafinil is a racemic compound, and the enantiomers have different pharmacokinetics where the elimination t½ of the R-isomer is three times that of the S-isomer in adult humans.

Linearity/non-linearity
The pharmacokinetic properties of modafinil are linear and time-independent. Systemic exposure increases in a dose proportional manner over the range of 200-600 mg.

Absorption
Modafinil is well-absorbed with peak plasma concentration reached approximately two to four hours after administration.
Food has no effect on overall modafinil bioavailability; however, absorption (tmax) may be delayed by approximately one hour if taken with food.

Distribution
Modafinil is moderately bound to plasma protein (approximately 60%), primarily to albumin, which indicates that there is a low risk of interaction with strongly bound drugs.

Biotransformation
Modafinil is metabolized by the liver. The chief metabolite (40 – 50% of the dose), modafinil acid, has no pharmacological activity.

Elimination
The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged (< 10% of the dose).
The effective elimination half-life of modafinil after multiple doses is about 15 hours.

Renal impairment

Severe chronic renal failure (creatinine clearance up to 20 mL/min) did not significantly affect the pharmacokinetics of modafinil administered at 200 mg, but exposure to modafinil acid was increased 9-fold. There is inadequate information to determine safety and efficacy of dosing in patients with renal impairment.

Hepatic impairment
In patients with cirrhosis, the oral clearance of modafinil was decreased by approximately 60%, and the steady-state concentration doubled, compared with values in healthy subjects. The dosage of modafinil should be reduced by half in patients with severe hepatic impairment.

Elderly population
There are limited data available on the use of modafinil in elderly patients. In view of the potential for lower clearance and increased systemic exposure, it is recommended that patients over 65 years of age commence therapy at 100 mg daily.

Paediatric population
For patients 6 to 7 years of age, the estimated half-life is approximately 7 hours and increases with increase in age until half-life values approach those in adults (approximately 15 hours). This difference in clearance is partially offset by the younger patients' smaller size and lower weight which results in comparable exposure following administration of comparable doses. Higher concentrations of one of the circulating metabolites, modafinil sulfone, are present in children and adolescents as compared to adults.

In addition, following repeat-dose administration of modafinil to children and adolescents, a time-dependent reduction in systemic exposure, which plateaus by approximately week 6 is observed. Once steady-state is reached, the pharmacokinetic properties of modafinil do not appear to change with continued administration for up to 1 year.

IV.3 Pharmacodynamics

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 direct-acting 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 agonist activity.

Modafinil does not appear to be a direct α_1-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 α_1-adrenoceptor antagonist, prazosin, in other assay systems (e.g. vas deferens) responsive to α-adrenoceptor agonists, modafinil is inactive.

In non-clinical models, equal wakefulness-promoting doses of methylphenidate and amphetamine increase neuronal activation throughout the brain, whereas modafinil unlike classical psychomotor stimulants, predominantly affects brain regions implicated in regulating arousal, sleep, wake and vigilance.

In humans, 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.

The efficacy of modafinil in patients with obstructive sleep apnoea (OSA) exhibiting excessive day time sleepiness despite treatment with continuous positive airways pressure (CPAP) has been studied in short term randomised controlled clinical trials. Although statistically significant improvements in sleepiness were noted, the magnitude of effect and response rate to modafinil was small when assessed by objective measurements and limited to a small sub-population of the treated patients. In light of this, and because of its known safety profile, the demonstrated benefit is

outweighed by the risks.

IV.4 Clinical Efficacy

The applicant submitted a clinical overview document outlining the clinical efficacy of the active substance. No additional clinical efficacy data were supplied, and this is appropriate for this type of application.

IV.5 Clinical Safety

No clinically relevant adverse events were noted during the bioequivalence trial which alter the risk-benefit profile of Modafinil.

Modafinil is currently subject to a yearly PSUR schedule at the HMA PSUR worksharing procedure. The next data-lock point is August 2012.

No additional risk minimisation measures are required for this active substance.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, the need for repetitive tests can be avoided. The applicant has submitted a suitable bioequivalence study, in which bioequivalence between the test product Modafinil, and the reference product Provigil was adequately demonstrated. No significant safety data emerged during this trial.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

From a quality perspective the overall assessment outcome of Prosentio 100mg and 200mg tablets is positive.

Prosentio 100mg and 200mg tablets are a generic form of Provigil 100mg and 200mg tablets. Provigil 100mg and 200mg tablets are well-known medicinal products with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Prosentio 100mg and 200mg tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.