Modafinil 100 mg and 200 mg Tablets

Modafinil

PL 06831/0271-72

UKPAR

TABLE OF CONTENTS

Modafinil 100 mg and 200 mg Tablets

PL 06831/0271-72

LAY SUMMARY

On 18th April 2013, the MHRA granted Marketing Authorisations (licences) for the medicinal products Modafinil 100 mg and 200 mg Tablets (PL 06831/0271-72). These medicines are only available on prescription from your doctor.

The active ingredient in the tablets is modafinil. Modafinil Tablets can be taken by adults who suffer from narcolepsy to help them to stay awake. Narcolepsy is a condition that causes excessive daytime sleepiness and a tendency to fall asleep suddenly in inappropriate situations (sleep attacks). Modafinil Tablets may improve your narcolepsy and reduce the likelihood that you will have sleep attack but there may still be other ways that you can improve your condition and your doctor will advise you.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Modafinil 100 mg and 200 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

Modafinil 100 mg and 200 mg Tablets

PL 06831/0271-72

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Modafinil 100 mg and 200 mg Tablets (PL 06831/0271-72) to Genus Pharmaceuticals Limited on 18th April 2013.

These prescription only medicines (POM) are 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.

These are national abridged applications for Modafinil 100 mg and 200 mg Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Provigil® 100 mg and 200 mg Tablets (PL 16260/0001-2), authorised to Cephalon UK Limited on 14th October 1997.

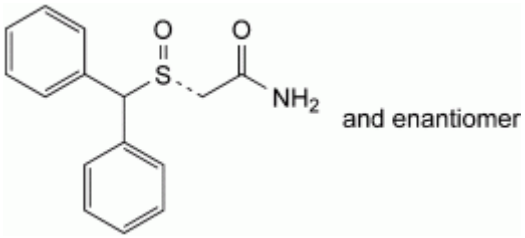
A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Modafinil
Chemical Names: 2-[(*RS*)-(Diphenylmethyl) sulfinyl]acetamide
2-(Benzhydrylsulfinyl)acetamide.

Structure:



Molecular Formula: $C_{15}H_{15}NO_2S$

Molecular Weight: 273.4

Appearance: white or almost white, crystalline powder
Solubility: very slightly soluble or practically insoluble in water, sparingly soluble in methanol, slightly soluble in ethanol (96 per cent)

Modafinil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance Modafinil are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients crospovidone (Type A), crospovidone (Type B), cellulose, microcrystalline, starch (maize) pregelatinised, povidone K-90**,** povidone K-30, lactose monohydrate, silica colloidal anhydrous, talc and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same

conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development
The objective of the development programme was to formulate robust, stable tablets containing 100mg and 200mg of modafinil which could be considered generic medicinal products of Provigil® 100 mg and 200 mg Tablets (Cephalon UK Limited).

Comparable dissolution and impurity profiles are provided for these products versus the originator products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale and has shown satisfactory results. The applicant has committed to perform process validation studies on the first three consecutive full- scale commercial batches of each tablet strength.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packed in:

- PVC/Aclar/Aluminium blisters
- OPA/Aluminium/PVC/Aluminium blisters.

Pack sizes for each strength are 10 and 30 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with no special storage condition is set. This is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner.

The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of modafinil are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

In support of these applications, the Marketing Authorisation holder has submitted a bioequivalence study:

A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Modafinil 200 mg tablets (Orchid Healthcare, India) and Provigil® 200 mg tablets (Cephalon UK Ltd, UK) in healthy human adult subjects under fasting conditions.

The blood samples were collected within one hour before dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dosing in both the periods. There was a washout period of 18 days between the dosings.

The pharmacokinetic results for modafinil are presented below:

Table 1 - Summary of Pharmacokinetic data for Modafinil

Dose = 200 mg

Provigil® (Reference product)

Pharmacokinetic Parameter	Geometric mean	Arithmetic Mean	Standard Deviation
AUC_{0-t} (µg.h/ml)	109.3478	112.4819	26.4864
$AUC_{0-\infty}$ (µg.h/ml)	119.3507	123.6611	32.7500
C_{max} (µg/ml)	7.5674	7.6737	1.2292

Modafinil (Test product)

Pharmacokinetic Parameter	Geometric mean	Arithmetic Mean	Standard Deviation
AUC_{0-t} (µg.h/ml)	109.4734	112.7475	27.4047
$AUC_{0-\infty}$ (µg.h/ml)	119.5080	124.0956	34.2364
C_{max} (µg/ml)	7.4532	7.5311	1.0856

Table 2 - Ratio and 90% Confidence Intervals of Test versus Reference for Modafinil

Pharmacokinetic Parameter	Ratio (%)	90% Confidence Intervals (%)
AUC_{0-t}	100.11	98.78 to 101.47
$AUC_{0-\infty}$	100.13	98.61 to 101.68
C_{max}	98.49	94.47 to 102.68

The results show that the 90% confidence intervals for AUC and C_{max} fell within the acceptable range (80.00-125.00%). Bioequivalence has been shown for the test

formulation (Modafinil 200 mg tablets) and the reference formulation (Provigil® 200 mg tablets).

As the 100 mg and 200 mg strengths of the products meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results of the study for the 200 mg formulation can be extrapolated to the other strength i.e. 100 mg tablets.

EFFICACY
No new efficacy data have been submitted and none are required for these applications.

SAFETY
No new safety data have been submitted and none are required for these applications.

EXPERT REPORT
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS
These are satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
These are satisfactory

MAA FORMS
These are satisfactory.

CONCLUSIONS
There are no objections to the approval of these products from a clinical point of view.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Modafinil 100 mg and 200 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY

No new data have been submitted and none are required for applications of these type.

Bioequivalence have been demonstrated between the applicant's Modafinil 200 mg Tablets and the reference product, Provigil® 200 mg Tablets. As the 100 mg and 200 mg strengths of the products meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results of the study for the 200 mg formulation can be extrapolated to the other strength i.e. 100 mg tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those for the reference products. Satisfactory labelling has also been submitted.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with modafinil is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Modafinil 100 mg and 200 mg Tablets

PL 06831/0271-72

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation applications on 13th April 2012.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 26th May 2012.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 3rd September 2012, 14th December 2012 and on the Clinical section on 25th January 2013.
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 15th November 2012, 11th January 2013 and on the Clinical section on 30th January 2013.
5	The applications were determined on 18th April 2013.

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

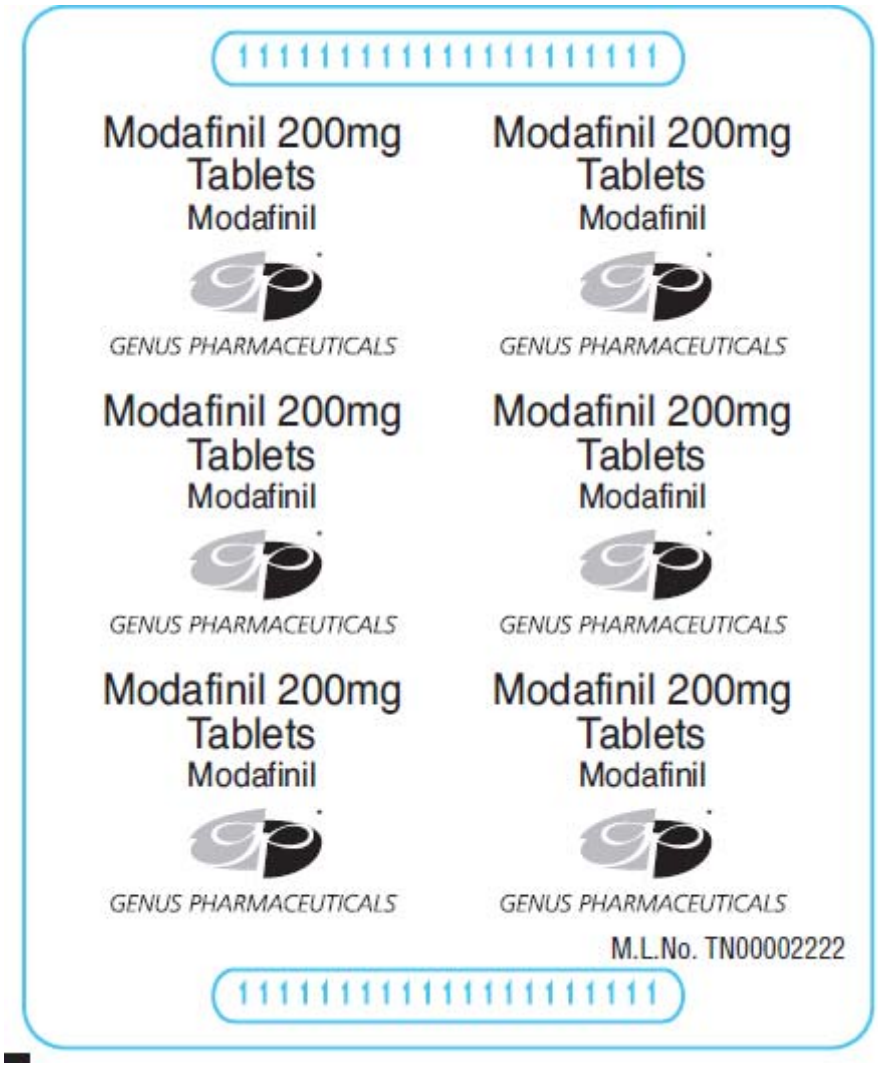
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING


Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 100mg Tablets
Modafinil
GENUS PHARMACEUTICALS
M.L.No. TN00002222


Modafinil
100mg Tablets
Modafinil
30 tablets
GENUS PHARMACEUTICALS
Modafinil
100mg Tablets
Modafinil
Each tablet contains 100mg modafinil.
Also contains lactose. See enclosed leaflet
for further information. This product does not
require any special storage conditions.
30 tablets
For oral use.
Read the package leaflet before use.
Keep out of sight and reach of children.
M.L.No. TN00002222
Batch No:
Exp:
POM
PL 06831/0271
MA holder:
Genus Pharmaceuticals,
Park View House,
65 London Road,
Newbury,
Berkshire RG14 1JN,
UK.
Please affix pharmacy label here
PIP XXX XXXX


Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
Modafinil 200mg Tablets
Modafinil
GENUS PHARMACEUTICALS
M.L.No. TN00002222

Braille text - modafinil #200 mg tablets