MODAFINIL 100MG TABLETS

PL 20117/0206

UKPAR

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MODAFINIL 100MG TABLETS

PL 20117/0206

LAY SUMMARY

On 6th June 2011, the MHRA granted a Marketing Authorisation (licence) for the medicinal product Modafinil 100mg Tablets. This medicine is 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 attacks 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 this application and it was, therefore, judged that the benefits of taking Modafinil 100mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

MODAFINIL 100MG TABLETS

PL 20117/0206

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a marketing authorisation for the medicinal product Modafinil 100mg Tablets (PL 20117/0206) to Morningside Healthcare Limited on the 6th June 2011. This is a prescription only medicine (POM) used in the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy. Excessive sleepiness is defined as difficulty in maintaining wakefulness and an increased likelihood of falling asleep in inappropriate situations.

This application was submitted as an abridged application according to Article 10.c of Directive 2001/83/EC, cross-referring to Modafinil 100mg Tablets (PL 24564/0005), held by Medochemie Limited, which was granted a marketing authorisation on 10th November 2010.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.

A detailed description of the applicant's pharmacovigilance system has been provided with this application and this is satisfactory.

No environmental risk assessment (ERA) has been undertaken, as this is not considered necessary. This is justified as it is not anticipated that the grant of this new marketing authorisation will result in an increase in the environmental exposure of the drug. The applicant's justification for absence of ERA is satisfactory.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 20117/0206
PROPRIETARY NAME: Modafinil 100mg Tablets
COMPANY NAME: Morningside Healthcare Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1 INTRODUCTION

This is an informed consent application for Modafinil 100mg Tablets, submitted under Article 10c of Directive 2001/83/EC. The application cross-refers to Modafinil 100mg Tablets (PL 24564/0005), approved on 10th November 2010 to the marketing authorisation holder, Medochemie Limited. The current application is considered valid.

2 MARKETING AUTHORISATION APPLICATION (MAA)

2.1 Name(s)

The proposed name of the product is Modafinil 100mg Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product is a tablet for oral use and contains 100mg of the active ingredient modafinil.

The tablets are packed in PVC/ Aluminium blisters; pack sizes of 20, 30, 60, 90 tablets are available. The packaging and pack sizes are the same as those for the reference product.

The proposed shelf life is 24 months with a storage condition of 'Store below 30˚C'. The shelf-life and storage condition are identical to those for the reference product and are satisfactory.

2.3 Legal status

This product is a prescription only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed marketing authorisation holder is Morningside Healthcare LTD, 115 Narborough Road, Leicester, UK

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross referenced product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross referenced product and the maximum batch size is stated.

2.8 Finished product/shelf-life specifications

The proposed finished product release and shelf-life specifications are in line with the details registered for the cross referenced product.

2.9 Drug substance specification

The proposed drug substance specifications conform to the current European Pharmacopoeia monograph for modafinil, and are in-line with those for the cross referenced product.

The European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability for the drug substance, modafinil, has been provided. The active substance manufacturers are in line with those for the cross referenced product.

2.10 TSE Compliance

No materials of human or animal origin have been used in the manufacture of this product. This is consistent with the cross referenced product.

2.11 Bioequivalence

No bioequivalence data are required to support this informed consent applications, as the proposed product is manufactured to the same formula utilising the same process as the cross reference product Modafinil 100mg Tablets (PL 24564/0005).

3 EXPERT REPORT

The applicant has included satisfactory expert reports for the application. Signed declarations and copies of the experts' CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product name. The appearance of the product is identical to that of the cross reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The proposed SmPC is consistent with the details registered for the cross reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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 it contains.

The proposed artwork complies with the relevant statutory requirements. In line with the current legislation, the applicant has also included the name of the product in

Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application are acceptable. The grant of a marketing authorisation is recommended.

NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for applications of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with those previously assessed for the cross reference product and, as such, have been judged to be satisfactory.

NON-CLINICAL

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

EFFICACY

This application is identical to the previously granted application for Modafinil 100mg Tablets (PL 24564/0005), granted to Medochemie Limited on 10th November 2010.

Quality, non-clinical and clinical expert statements have been provided, together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective cross reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant's product is identical to the cross reference product. Extensive clinical experience with modafinil is considered to have demonstrated the therapeutic values of the compound. The risk benefit is, therefore, considered to be positive.

MODAFINIL 100MG TABLETS

PL 20117/0206

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 3rd February 2011
2	Following standard checks and communication with the applicant the MHRA considered the application is valid on 18th February 2011
3	The application was determined on 6th June 2011

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Modafinil 100mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Modafinil 100mg
Excipient: Each tablet contains 84.0 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, round, biconvex, tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MODAFINIL 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.

4.2 Posology and method of administration

Treatment should be initiated by or under the supervision of a physician with appropriate knowledge of indicated disorders (see section 4.1).
A diagnosis of narcolepsy should be made according to the International Classification of Sleep Disorders (ICSD2) guideline.
Patient monitoring and clinical assessment of the need for treatment should be performed on a periodic basis.
Posology
The recommended starting daily dose is 200 mg. The total daily dose may be taken as a single dose in the morning or as two doses in the morning and at noon, according to physician assessment of the patient and the patient's response.
Doses of up to 400mg in one or two divided doses can be used in patients with insufficient response to the initial 200mg modafinil dose.

Long-term use
Physicians prescribing modafinil for an extended time should periodically re-evaluate the long-term use for the individual patients as the long-term efficacy of modafinil has not been evaluated (> 9 weeks).

Patients with renal impairment
There is inadequate information to determine safety and efficacy of dosing in patients with renal impairment (see section 5.2).

Patients with hepatic impairment
The dose of modafinil should be reduced by half in patients with severe hepatic impairment (see section 5.2).

Elderly
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
Modafinil should not be used in children aged less than 18 years old because of safety and efficacy concerns (see section 4.4).

Method of administration
For oral use. Tablets should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

4.4 Special warnings and precautions for use

Diagnosis of sleep disorders
Modafinil should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of narcolepsy, has been made in accordance with ICSD diagnostic criteria. Such an evaluation usually consists, in addition to the patient's history, sleep measurements testing in a laboratory setting and exclusion of other possible causes of the observed hypersomnia.
Serious rash, including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms
Serious rash requiring hospitalisation and discontinuation of treatment has been reported with the use of modafinil, occurring within 1 to 5 weeks after treatment initiation. Isolated cases have also been reported after prolonged treatment (e.g., 3 months). In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in paediatric patients (age <17
years); this includes serious rash. No serious skin rashes have been reported in adult clinical trials (0 per 4,264) of modafinil. Modafinil should be discontinued at the first sign of rash and not restarted (see section 4.8).
Rare cases of serious or life-threatening rash, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience.
Paediatric use
Because safety and effectiveness in controlled studies in children have not been established and because of the risk of serious cutaneous hypersensitivity and psychiatric adverse reactions, the use of modafinil is not recommended.
Multi-organ hypersensitivity reaction
Multi-organ hypersensitivity reactions, including at least one fatality in post-marketing experience, have occurred in close temporal association to the initiation of modafinil. Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated
manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia.
Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.
If a multi-organ hypersensitivity reaction is suspected, modafinil should be discontinued.
Psychiatric disorders
Patients should be monitored for the development of de novo or exacerbation of pre-existing psychiatric disorders (see below and Section 4.8) at every adjustment of dose and then regularly during treatment. If psychiatric symptoms develop in association with modafinil treatment, modafinil should be discontinued and not restarted. Caution should be exercised in giving modafinil to patients with a history of psychiatric disorders including psychosis, depression , mania, major anxiety, agitation, insomnia or substance abuse (see below).
Anxiety
Modafinil is associated with the onset or worsening of anxiety. Patients with major anxiety should only receive treatment with modafinil in a specialist unit.
Suicide-related behaviour
Suicide-related behaviour (including suicide attempts and suicidal ideation) has been reported in patients treated with modafinil. Patients treated with modafinil should be carefully monitored for the appearance or worsening of suicide-related behaviour. If suicide-related symptoms develop in association with modafinil, treatment should be discontinued.

Psychotic or manic symptoms
Modafinil is associated with the onset or worsening of psychotic symptoms or manic symptoms (including hallucinations, delusions, agitation or mania). Patients treated with modafinil should be carefully monitored for the appearance or worsening of psychotic or manic symptoms. If psychotic or manic symptoms occur, discontinuation of modafinil may be required.
Bipolar disorders
Care should be taken in using modafinil in patients with co-morbid bipolar disorder because of concern for possible precipitation of a mixed/manic episode in such patients.
Aggressive or hostile behaviour
The onset or worsening of aggressive or hostile behaviour can be caused by treatment with modafinil.
Patients treated with modafinil should be carefully monitored for the appearance or worsening of aggressive or hostile behaviour. If symptoms occur, discontinuation of modafinil may be required.
Cardiovascular risks
An ECG is recommended in all patients before Modafinil treatment is initiated. Patients will abnormal findings should receive further specialist evaluation and treatment before Modafinil treatment is considered.
Blood pressure and heart rate should be regularly monitored in patients receiving modafinil. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension and not restarted until the condition has been adequately evaluated and treated.
Modafinil tablets are not recommended in patients with a history of left ventricular hypertrophy or cor pulmonale and in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia.
Insomnia
Because modafinil promotes wakefulness, caution should be paid to signs of insomnia.
Maintenance of sleep hygiene
Patients should be advised that modafinil is not a replacement for sleep and good sleep hygiene should be maintained. Steps to ensure good sleep hygiene may include a review of caffeine intake.
Patients using steroidal contraceptives
Sexually active women of child-bearing potential should be established on a contraceptive programme before taking modafinil. Since the effectiveness of steroidal contraceptives may be reduced when used with modafinil, alternative or concomitant methods of contraception are recommended, and for two months after discontinuation of modafinil (also see 4.5 with respect to potential interaction with steroidal contraceptives).
Abuse, misuse, diversion
Whilst studies with modafinil have demonstrated a potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded.
Caution should be exercised in administering modafinil to patients with history of alcohol, drug or illicit substance abuse.
MODAFINIL tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Modafinil may increase its own metabolism via induction of CYP3A4/5 activity but the effect is modest and unlikely to have significant clinical consequences.
Anticonvulsants: Co-administration of potent inducers of CYP activity, such as carbamazepine and phenobarbital, could reduce the plasma levels of modafinil. Due to a possible inhibition of CYP2C19 by modafinil and suppression of CYP2C9 the clearance of phenytoin may be decreased when modafinil is administered concomitantly. Patients should be monitored for signs of phenytoin toxicity, and repeated measurements of phenytoin plasma levels may be appropriate upon initiation or discontinuation of treatment with modafinil.
Steroidal contraceptives: The effectiveness of steroidal contraceptives may be impaired due to induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception are recommended for patients treated with modafinil. Adequate contraception will require continuation of these methods for two months after stopping modafinil.

Antidepressants: A number of tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of a Caucasian population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19, lower doses of antidepressants may be required in such patients.
Anticoagulants: Due to possible suppression of CYP2C9 by modafinil the clearance of warfarin may be decreased when modafinil is administered concomitantly. Prothrombin times should be monitored regularly during the first 2 months of modafinil use and after changes in modafinil dosage.
Other medicinal products: Substances that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol and omeprazole may have reduced clearance upon co-administration of modafinil and may thus require dosage reduction. In addition, in vitro induction of CYP1A2, CYP2B6 and CYP3A4/5 activities has been observed in human hepatocytes, which were it to occur in vivo, could decrease the blood levels of drugs metabolised by these enzymes, thereby possibly decreasing their therapeutic effectiveness. Results from clinical interaction studies suggest that the largest effects may be on substrates of CYP3A4/5 that undergo significant presystemic elimination, particularly via CYP3A enzymes in the gastrointestinal tract. Examples include ciclosporin, HIV-protease inhibitors, buspirone, triazolam, midazolam and most of the calcium channel blockers and statins. In a case report, a 50% reduction in ciclosporin concentration was observed in a patient receiving ciclosporin in whom concurrent treatment with modafinil was initiated.

4.6 Pregnancy and lactation

Pregnancy
There is limited data on the use of modafinil in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).
Modafinil is not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception. As modafinil may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see section 4.5).
Breastfeeding
Available pharmacodynamic/toxicological data in animals have shown excretion of Modafinil/metabolites in milk (for details see 5.3).
Modafinil should not be used during breast feeding.
Fertility
No data on fertility are available.

4.7 Effects on ability to drive and use machines

Patients with abnormal levels of sleepiness who take modafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity Undesirable effects such as blurred vision or dizziness might also affect ability to drive (see section 4.8).

4.8 Undesirable effects

The following adverse reactions have been reported in clinical trials and/or post-marketing experience. The frequency of adverse reactions considered at least possibly related to treatment, in clinical trials involving 1561 patients taking modafinil were as follows: very common (≥1/10), common (≥1/100 to ≤1/10), uncommon (≥1/1000 to ≤1/100), unknown (cannot be estimated from the available data). The most commonly reported adverse drug reaction is headache, affecting approximately 21% of patients. This is usually mild or moderate, dose-dependent and disappears within a few days.
Infections and infestations
Uncommon: pharyngitis, sinusitis
Blood and lymphatic system disorders
Uncommon: eosinophilia, leucopenia
Immune system disorders
Uncommon: minor allergic reaction (e.g., hayfever symptoms)
Unknown: Angioedema, urticaria (hives). Hypersensitivity reactions (characterised by features such as fever, rash, lymphadenopathy and evidence of other concurrent organ involvement).

Metabolism and nutrition disorders
Common: decreased appetite
Uncommon: hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite,
Psychiatric disorders
Common: nervousness, insomnia, anxiety, depression, abnormal thinking, confusion.
Uncommon: sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, abnormal dreams, agitation, aggression, suicidal ideation.
Rare: hallucinations, mania, psychosis
Unknown: delusions.
Nervous system disorders
Very common: headache
Common: dizziness, somnolence, paraesthesia
Uncommon: dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion
Eye disorders
Common: blurred vision
Uncommon: abnormal vision, dry eye
Cardiac disorders
Common: tachycardia, palpitation
Uncommon: extrasystoles, arrhythmia, bradycardia
Vascular disorders
Common: vasodilatation
Uncommon: hypertension, hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, increased cough, asthma, epistaxis, rhinitis
Gastrointestinal disorders
Common: abdominal pain, nausea, dry mouth, diarrhoea, dyspepsia, constipation
Uncommon: flatulence, reflux, vomiting, dysphagia, glossitis, mouth ulcers
Skin and subcutaneous tissue disorders
Uncommon: sweating, rash, acne, pruritis
Unknown: serious skin reactions, including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Musculoskeletal and connective tissue disorders
Uncommon: back pain, neck pain, myalgia, myasthenia, leg cramps, arthralgia, twitch
Renal and urinary disorders
Uncommon: abnormal urine, urinary frequency
Reproductive system and breast disorders
Uncommon: menstrual disorder
General disorders and administration site conditions
Common: asthenia, chest pain
Uncommon: peripheral oedema, thirst
Investigations
Common: abnormal liver function tests, dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed.
Uncommon: abnormal ECG, weight increase, weight decrease

4.9 Overdose

Symptoms most often accompanying modafinil overdose, alone or in combination with other drugs have included: insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.
Management
Induced emesis or gastric lavage should be considered. Hospitalisation and surveillance of psychomotor status; cardiovascular monitoring or surveillance until the patient's symptoms have resolved are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptic, centrally acting sympathomimetic, ATC code: N06BA

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 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, 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.

5.2 Pharmacokinetic properties

Modafinil is a racemic compound, and the enantiomers have different pharmacokinetics where the elimination t1/2 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.

5.3 Preclinical safety data

Toxicology studies by single and repeated dosing have revealed no particular toxic action in animals.

Modafinil is not considered to be mutagenic or carcinogenic.

Reproductive toxicity studies conducted in rats and rabbits showed an increased incidence in skeletal variations (changes in the numbers of ribs and delayed ossification), embryo-fetal lethality (periimplantation loss and resorptions) and some evidence of an increase in stillbirths (rats only), in the absence of maternal toxicity, at clinically relevant exposures. There was no effect on fertility and no evidence of teratogenic potential at systemic exposures equivalent to the maximum recommended human dose.

Reproduction toxicity studies revealed no effect on fertility, nor any teratogenic effect, nor any effect on viability, growth or development of the offspring.

Animal exposure to modafinil, based on actual plasma levels in the general toxicology, reproductive and carcinogenicity studies, was less than or similar to that expected in humans. This circumstance is the result of metabolic auto-induction noted in the pre-clinical studies. However, animal exposure on a mg/kg dose basis to modafinil in the general toxicology, reproductive and carcinogenicity studies was greater than the expected exposure, calculated on a similar basis, in humans.

In the rat peri-post-natal study, modafinil concentration in milk was about 11.5 times higher than in plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Croscarmellose sodium (E468)
Aluminium magnesium silicate
Povidone K 90 (E1201)
Talc (E553b)
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30ºC

6.5 Nature and contents of container
The tablets are packed in PVC/ Aluminium blisters; boxes of 20, 30, 60, 90 tablets are available.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
MORNINGSIDE HEALTHCARE LTD
115 NARBOROUGH ROAD
LEICESTER
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0206

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/06/2011

10 DATE OF REVISION OF THE TEXT
06/06/2011

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MODAFINIL 100mg tablets

Modafinil

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT MODAFINILTABLETS ARE AND WHAT THEY USED FOR

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 attacks but there may still be other ways that you can improve your condition and your doctor will advise you.

2. BEFORE YOU TAKE MODAFINIL TABLETS

DO not take Modafinil Tablets if you:
- Are **allergic** (hypersensitive) to modafinil, or to any of the other ingredients of these tablets (see Section 6 'What Modafinil Tablets contains').
- Have an **irregular heartbeat**.
- Have **uncontrolled, moderate to severe high blood pressure** (hypertension).

Take special care with Modafinil Tablets if you:
- Have any **heart problems** or **high blood pressure**. Your doctor will need to check these regularly while you are taking Modafinil Tablets.
- Have ever had **depression, low mood, anxiety, psychosis** (loss of contact with reality) or **mania** (over-excitement or feeling of extreme happiness) or **bipolar disorder** because Modafinil Tablets may make your condition worse.
- Have **kidney or liver problems** (because you will need to take a lower dose).
- Have had **alcohol** or **drug problems** in the past.

Children aged less than 18 years should not take this medicine.

Other things to talk to your doctor or pharmacist about
- Some people have reported having **suicidal** or **aggressive thoughts** or **behaviour** while taking this medicine. **Tell your doctor straight away** if you notice that you are becoming **depressed, feel aggressive or hostile** towards other people or have **suicidal thoughts** or other changes in your behaviour (see section 4). You may want to consider asking a family member or close friend to help you look out for signs of depression or other changes in your behaviour.
- This medicine has the potential for you to become reliant (dependent) on it after long-term use.

If you need to take it for a long time your doctor will check regularly that it is still the best medicine for you.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription. Modafinil Tablets and certain other medicines can affect each other and your doctor may need to adjust the doses that you are taking. It is especially important if you are taking any of the following medicines as well as Modafinil Tablets:
- Hormonal contraceptives (including the contraceptive pill, implants, intrauterine devices (IUDs) and patches). You will need to consider other birth control methods while taking Modafinil Tablets, and for two months after stopping treatment, because Modafinil Tablets reduces their effectiveness.
- Omeprazole (for acid reflux, indigestion or ulcers).
- Antiviral medicines to treat HIV infection (protease inhibitors e.g. indinavir or ritonavir).
- Ciclosporin (used to prevent organ transplant rejection, or for arthritis or psoriasis).
- Medicines for epilepsy (e.g. carbamazepine, phenobarbital or phenytoin).
- Medicines for depression (e.g. amitriptyline, citalopram or fluoxetine) or anxiety (e.g. diazepam).
- Medicines for thinning the blood (e.g. warfarin). Your doctor will monitor your blood clotting times during treatment.
- Calcium channel blockers or beta-blockers for high blood pressure or heart problems (e.g. amlodipine, verapamil or propranolol).
- Statin medicines for lowering cholesterol (e.g. atorvastatin or simvastatin).

Pregnancy and breastfeeding
If you are pregnant (or think that you may be), are planning to become pregnant or are breast-feeding you should not take Modafinil Tablets. It is not known if your medicine may harm your unborn baby.
Talk to your doctor about the birth control methods that will be right for you while you are taking Modafinil Tablets (and for two months after stopping) or if you have any other concerns.

Driving and using machines
Modafinil Tablets can cause blurred vision or dizziness in up to 1 in 10 people.
If you are affected or you find that while using this medication you still feel very sleepy, do not attempt to drive or operate machinery.

Important information about some of the ingredients of Modafinil Tablets
These tablets contain lactose. If your doctor has told you that you have an intolerance to some sugars, you should consult your doctor before taking this medicine.

3. HOW TO TAKE MODAFINIL TABLETS

Always take Modafinil Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Modafinil Tablets should be swallowed whole with water.
Adults
The usual dose is 200 mg a day. This can be taken once daily (in the morning) or divided into two doses a day (100 mg in the morning and 100 mg at midday).
Your doctor in some cases may decide to increase your daily dose up to 400 mg.
Elderly patients (over 65 years of age)
The usual dose is 100 mg a day. This can be taken once daily (in the morning) or divided into two doses a day (50 mg in the morning and 50 mg at midday).
Your doctor will only increase your dose (up to the maximum 400 mg a day) provided that you do not have any liver or kidney problems.

Adults with severe kidney and liver problems
The usual dose is 100 mg a day.
Your doctor will review your treatment regularly to check that it is right for you.

If you take more Modafinil Tablets than you should:
If you take too many tablets you may feel sick, restless, disorientated, confused or excited. You may also have difficulty sleeping, diarrhoea, hallucinations (sensing things that are not real), chest pain, a change in the speed of your heart beat or an increase in blood pressure Contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. Take this leaflet and any remaining tablets with you.

If you forget to take Modafinil Tablets:
If you forget to take your medicine take the next dose at the usual time, do not take a double dose to make up for the forgotten one.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Modafinil Tablets **can** cause side effects although not everybody gets them.

Stop taking this medicine and **tell your doctor straight away** if:
- You have sudden difficulty breathing or wheeziness or your face, mouth or throat begins to swell.
- You notice a skin rash or itching (especially if it affects your whole body). Severe rashes may cause blistering or peeling of the skin, ulcers in your mouth, eyes, nose or genitals. You may also have a high temperature (fever) and abnormal blood test results.
- You feel any change in your mental health and wellbeing. The signs may include:
  - mood swings or abnormal thinking,
  - aggression or hostility,
  - forgetfulness or confusion,
  - feeling of extreme happiness,
  - over-excitement or hyperactivity,
  - anxiety or nervousness,
  - depression, suicidal thoughts or behaviour,
  - agitation or psychosis (a loss of contact with reality which may include delusions or sensing things that are not real), feeling detached or numb, or personality disorder.

Other side effects include the following:
Very common side effects (affecting more than 1 in 10 people):
- Headache.

Common side effects (affecting fewer than 1 in 10 people):
- Dizziness.
- Sleepiness, extreme tiredness or difficulty sleeping (insomnia).
- Awareness of your heart beat, which may be faster than normal.
- Chest pain
- Flushing.
- Dry mouth.
- Loss of appetite, feeling sick, stomach pain, indigestion, diarrhoea or constipation.
- Weakness.
- Numbness or tingling of the hands or feet ('pins and needles').
- Blurred vision.
- Abnormal blood test results showing how your liver is working (increased liver enzymes).

Uncommon side effects (affecting fewer than 1 in 100 people):
- Back pain, neck pain, muscle pain, muscle weakness, leg cramps, joint pain, twitching or tremor.
- Vertigo (spinning sensation).
- Difficulty moving muscles smoothly or other movement problems, muscle tension, coordination
- problems.
- Hayfever symptoms including itchy/runny nose or watery eyes.
- Increased cough, asthma or shortness of breath.
- Skin rash, acne or itchy skin.
- Sweating.
- Changes in blood pressure (high or low), abnormal heart trace (ECG), and irregular or unusually
- slow heart beat.
- Difficulty swallowing, swollen tongue or mouth ulcers.
- Excess wind, reflux (bringing back fluid from the stomach), increased appetite, weight changes, thirst or taste alteration.
- Being sick (vomiting)
- Migraine.
- Speech problems.
- Diabetes with increased blood sugar.
- High blood cholesterol.
- Swollen hands and feet.
- Disrupted sleep or abnormal dreams,
- Loss of sex drive.
- Nose bleed, sore throat or inflamed nasal passages (sinusitis).
- Abnormal vision or dry eyes.
- Abnormal urine or more frequent urination.
- Abnormal periods.
- Abnormal blood test results showing that the numbers of your white blood cells have changed.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MODAFINIL TABLETS

Keep out of the reach and sight of children.

Store below 30ºC

Do not use after the expiry date stated on the carton and blister. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Modafinil Tablets contains:
- The active ingredient is modafinil. Each tablet contains modafinil 100 mg.
- The other ingredients (excipients) are: Lactose monohydrate, maize starch, croscarmellose sodium (E468), aluminium magnesium silicate, povidone K 90 (E1201), talc(E553b), magnesium stearate(E572).

What Modafinil Tablets looks like and the contents of the pack
Modafinil Tablet is a white, round, biconvex, tablet.
The tablets are packed in PVC/AL blisters; packs of 20, 30, 60, 90 tablets are available.

Marketing Authorisation Holder:
Morningside Healthcare Ltd
115 Narborough Road, Leicester
LE3 0PA, U.K.

Manufacturer:
Medochemie Ltd.,
1-10 Constantinoupoleos,
3011 Limassol, Cyprus

This leaflet was approved in 02/2011

LABELLING


Modafinil 100mg Tablet
Modafinil
Morningside Healthcare Ltd
Modafinil 100mg Tablet
Modafinil
Morningside Healthcare Ltd
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Morningside Healthcare Ltd
Modafinil 100mg Tablet
Modafinil
Morningside Healthcare Ltd
Embossing Space for Batch Details
Exp. & Lot


Modafinil 100mg Tablets
Dispensing label to be affixed here
Each tablet contains Modafinil 100mg
Contains lactose. For further information see package leaflet.
For oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 30°C
Batch Over Printing Panel
Batch No.:
Exp.:
MA Holder: Morningside Healthcare Limited
115 Narborough Road, Leicester, LE3 0PA, U.K.
PL 20117/0206
POM
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100mg
20 Tablets
Modafinal 100 mg Tablets
Modafinil
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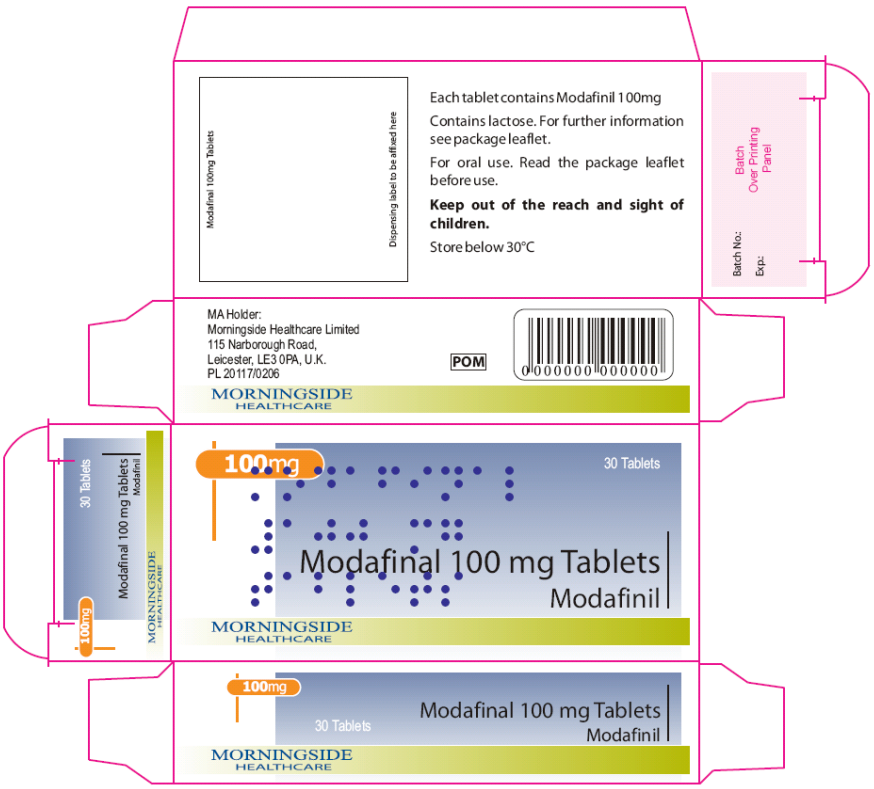
Modafinal 100mg Tablets
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115 Narborough Road,
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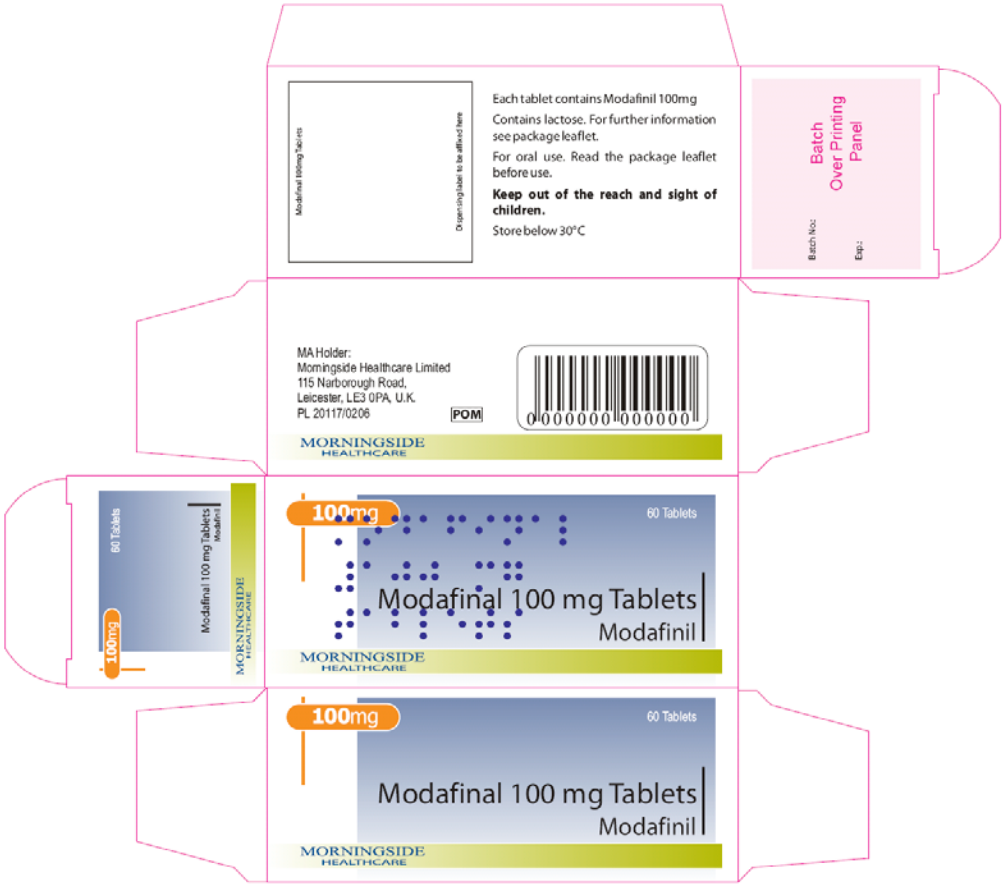
Modafinil
100mg
Modafinal 100 mg Tablets
Modafinil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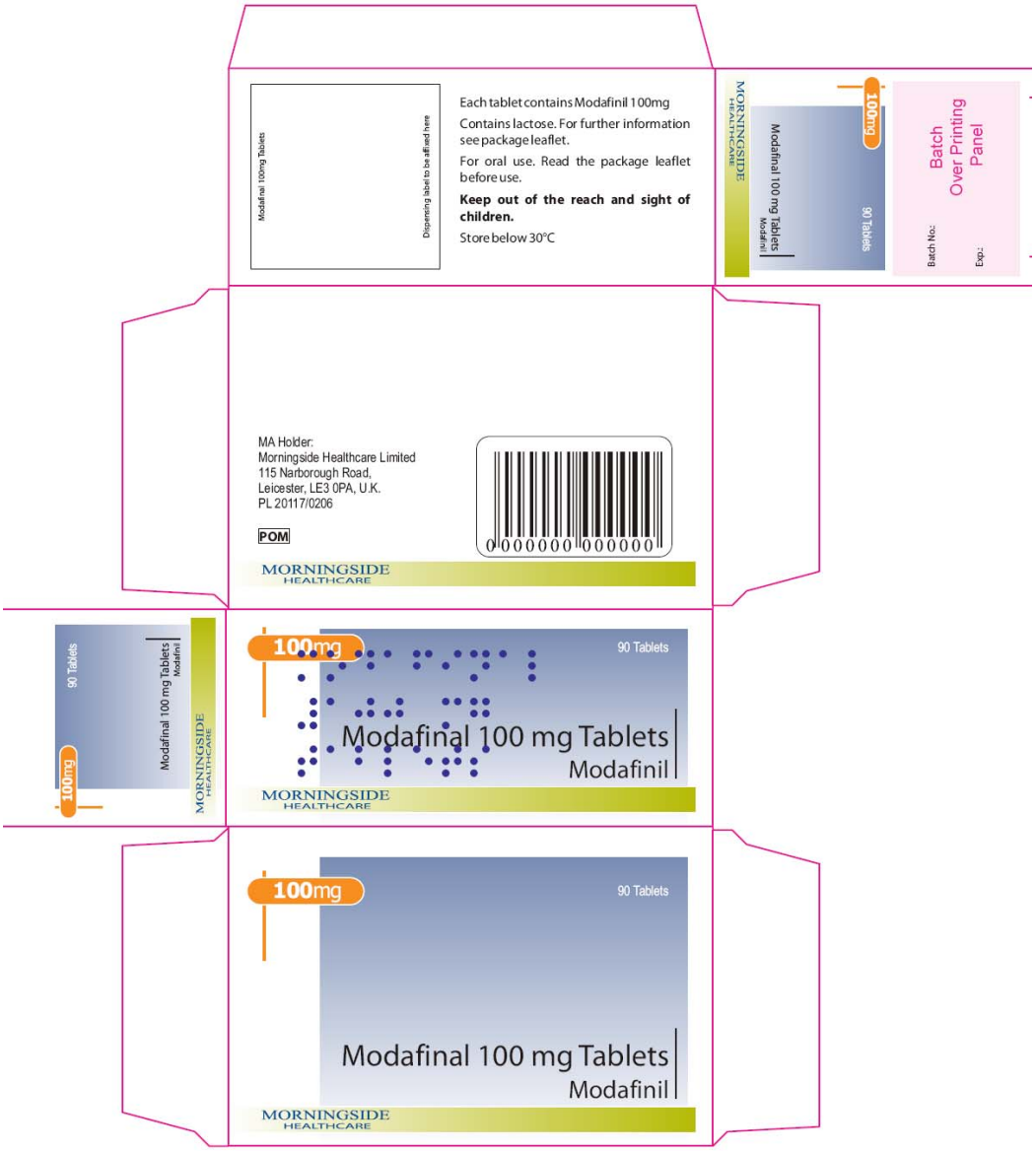
60 Tablets
Modafinil 100 mg Tablets
Modafinil
100mg
Modafinal 100 mg Tablets
Modafinil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