Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prosentio 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg modafinil.

Excipient(s) with known effect:

Each tablet contains 53.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White to off white coloured, capsule-shaped tablet debossed with 'M'on one side and '100 MG' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prosentio 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 listed in section 6.1.

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 re-started** (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 population
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 with 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 corpulmonale 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,diversionanddependence
There have been studies with modafinil that 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 a history of psychiatric disorders (see above), history of alcohol, drug or illicit substance abuse.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Fertility, pregnancy and lactation

Pregnancy

Based on limited human experience from a pregnancy registry and spontaneous reporting modafinil is suspected to cause congenital malformations when administered during pregnancy.

Studies in animals have shown reproductive toxicity (see section 5.3).

Prosentio should not be used during pregnancy.

Women of childbearing potential have to use effective contraception. As modafinil may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see sections 4.4 and 4.5).

Breast-feeding
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), anaphylaxis

Metabolism and nutrition disorders
Common: decreased appetite
Uncommon: hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite

Psychiatric disorders
Common: nervousness, insomnia, anxiety, depression, abnormal thinking, confusion, irritability
Uncommon: sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, abnormal dreams, agitation, aggression, suicidal ideation, psychomotor hyperactivity
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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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 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 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 adrenoceptor antagonist, prazosin, in other assay systems (e.g. vas deferens) responsive to 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.

Three epidemiological studies all utilizing a long-term observational inception cohort design were conducted in administrative databases assessing the cardiovascular and cerebrovascular risk of modafinil. One of the three studies suggested an increase in the incidence rate of stroke in modafinil treated patients compared to patients not treated with modafinil, however, results across the three studies were not consistent.

5.2 Pharmacokinetic properties

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.

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-foetal lethality (peri-implantation 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

Crospovidone
Starch, pregelatinised
Cellulose, microcrystalline
Povidone
Lactose monohydrate
Silica, colloidal anhydrous
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1. PVC/Aclar/Aluminium blister
2. Aluminium/Aluminium blister

Packs sizes: 10, 14, 15, 20, 28, 30, 56, 60, 90, 100 and 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/190/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 2012

Date of last renewal: 5th July 2017

10 DATE OF REVISION OF THE TEXT

July 2022