IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0749/018/001
Case No: 2052639

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Teva Pharma B.V.

Computerweg 10, **3542 DR Utrecht**, **Netherlands**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Modafinil Teva 100mg tablet

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/11/2008** until **07/09/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Modafinil Teva 100mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of modafinil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round-shaped tablet, debossed with the numbers “93” on one side and “7228” on the other side of the tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Modafinil is indicated for the treatment of excessive daytime sleepiness associated with narcolepsy
Therapy with modafinil should only be initiated by specialists once an accurate diagnosis of narcolepsy has been established.

4.2 Posology and method of administration

Adults
The recommended daily dose is 200 - 400 mg, commencing at 200 mg and titrated according to clinical response. Modafinil may be taken as two divided doses in the morning and at noon, or as a single dose in the morning, according to physician assessment of the patient and the patient's response.

Elderly
There are limited data available on the use of modafinil in elderly patients. In view of the generally lower hepatic and renal clearance expected in an elderly population, it is recommended that patients over 65 years of age should commence therapy at 100 mg daily. The maximum dose of 400 mg per day should only be used in the absence of renal or hepatic impairment.

Hepatic and renal failure
The dose in patients with severe hepatic or renal failure should be reduced by half (100 – 200 mg/day) (see section 4.4).

Children and adolescents
Because safety and effectiveness in controlled studies in children and adolescents have not been established the use of modafinil is not recommended in these patients (see section 4.4).

Method of administration
Tablets should be swallowed whole, with fluid, with or without food.

4.3 Contraindications

Modafinil is contraindicated in patients with hypersensitivity to modafinil or any of the excipients.

4.4 Special warnings and precautions for use

Patients with major anxiety should only receive treatment with modafinil in a specialist unit.

Caution is also required when treating patients with a history of psychosis.

Blood pressure and heart rate should be monitored in hypertensive patients.

It is recommended that modafinil not be used in patients with a history of left ventricular hypertrophy or cor pulmonale. Modafinil should not be used 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.
The ECG of patients with cardiovascular diseases should be monitored regularly.

Whilst studies with modafinil have indicated a relatively low potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded. Modafinil should therefore be avoided in patients with a known tendendy towards substance abuse.

Caution is required when treating patients with severe hepatic or renal failure (see section 4.2).

When oral contraceptives are used, a product containing 50 micrograms or more of ethinyloestradiol should be taken or alternative/concomitant methods of contraception should be considered. Adequate contraception will require continuation of these methods for two cycles after stopping modafinil (see section 4.5).

Warning for athletes:
This medicinal product contains an active substance which can cause positive results in doping tests.

Because safety and effectiveness in controlled studies in children and adolescents have not been established the use of modafinil is not recommended in these patients (see section 4.2).

Patients should be advised that modafinil is not a replacement for sleep and good sleep hygiene should be maintained.

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 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).

Psychiatric adverse experiences, including suicidal ideation, have been reported in patients treated with Modafinil. In such circumstances, Modafinil should be discontinued and not re-started. Caution should be exercised in administering Modafinil to patients with a history of psychosis, depression or mania, given the possible emergence or exacerbation of psychiatric symptoms (see section 4.8).

Caution should also be exercised in administering Modafinil to patients with history of alcohol, drug or illicit substance abuse.

4.5 Interaction with other medicinal products and other forms of interaction

In preclinical studies, modafinil-induced wakefulness could be attenuated by the α_1-adrenergic receptor antagonist, prazosin. Although clinical studies have not been performed, the possibility cannot be excluded that the administration of α_1-adrenergic receptor antagonists, such as prazosin, and α_2-adrenergic receptor agonists, such as clonidine, could decrease the effect of modafinil.

Caution should be exercised when modafinil is used concomitantly with noradrenergic agents, such as maprotiline,

venlafaxine, reboxetine, since these combinations have not been studied.

The use of alcohol is conjunction with modafinil has not been studied, and should therefore be avoided during treatment.

No interaction was observed when low doses of clomipramine, methylphenidate or dexamphetamine were administered for a short period concomitantly with modafinil.

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.

Oral contraceptives: The effectiveness of oral contraceptives may be impaired due to induction of CYP3A4/5 by modafinil. When oral contraceptives are used, a product containing 50 micrograms or more of ethinyloestradiol should be taken or alternative/concomitant methods of contraception should be considered. Adequate contraception will require continuation of these methods for two cycles 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: Medicinal products 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 substances 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 cyclosporin, HIV-protease inhibitors, buspirone, triazolam, midazolam and most of the calcium channel blockers and statins. In a case report, a 50% reduction in cyclosporin concentration was observed in a patient receiving cyclosporin in whom concurrent treatment with modafinil was initiated.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of modafinil in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Modafinil should not be used during pregnancy unless clearly necessary.

Lactation
It is unknown whether modafinil is excreted in human breast milk. Animal studies have shown excretion of modafinil in breast milk. A decision on whether to continue / discontinue breast-feeding or to continue / discontinue therapy with modafinil should be made taking into account the benefit of breast-feeding to the child and the benefit of modafinil therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Undesirable effects such as blurred vision or dizziness might affect ability to drive (see section 4.8).

4.8 Undesirable effects

The adverse events considered to be at least possibly related to treatment, from clinical trials involving 1561 patients taking modafinil were as follows (very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (≤ 1/10000), not known (cannot be estimated from the available data)).
The most commonly reported adverse reaction is headache, affecting approximately 21% of patients. This is usually mild or moderate, dose-dependent and disappears within a few days.

Blood and the lymphatic system disorders
Uncommon: eosinophilia, leucopenia

Endocrine disorders
Uncommon: diabetes mellitus

Metabolic and nutritional disorders
Common: abnormal liver function tests, decreased appetite, anorexia
Dose-related increases in alkaline phosphatase and gamma glutamyl transferase have been observed.
Uncommon: peripheral oedema, weight increase, weight decrease, hyperglycaemia, hypercholesterolaemia

Psychiatric disorders
Common: nervousness, anxiety, depression, abnormal thinking, confusion
Uncommon: agitation, emotional lability, hostility, aggressive behaviour, depersonalisation, personality disorder, aggression
Unknown: psychosis, mania, delusions, hallucinations and suicidal ideation.

Nervous system disorders
Very common: headache
Common: insomnia, dizziness, somnolence, paraesthesia, asthenia
Uncommon: sleep disorder, dyskinesia, hypertonia, hyperkinesia, amnesia, abnormal dreams, migraine, tremor, vertigo, decreased libido, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder
Very rare: orofacial dyskinesia

Eye disorders
Common: blurred vision
Uncommon: abnormal vision, dry eye

Cardiac disorders
Common: tachycardia, palpitation
Uncommon: hypertension, abnormal ECG, extrasystoles, arrhythmia, bradycardia, hypotension

Vascular disorders
Common: vasodilatation

Respiratory, thoracic and mediastinal disorders
Uncommon: pharyngitis, dyspnoea, rhinitis, increased cough, asthma, epistaxis, sinusitis

Gastrointestinal disorders
Common: nausea, dry mouth, diarrhoea, dyspepsia, constipation, abdominal pain
Uncommon: flatulence, reflux, vomiting, increased appetite, thirst, dysphagia, glossitis, mouth ulcers, taste perversion

Skin and subcutaneous tissue disorders
Uncommon: sweating, rash, acne, pruritus
Unknown: serious skin reactions, including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Musculoskeletal, connective tissue and bone disorders
Uncommon: myalgia, muscle weakness, leg cramps, arthralgia, twitch, back pain, neck pain

Renal and urinary disorders
Uncommon: abnormal urine, urinary frequency, menstrual disorder

General disorders and administration site conditions
Common: chest pain
Uncommon: minor allergic reaction (e.g., hayfever symptoms)

Immune System Disorders
Unknown: Hypersensitivity reactions (characterised by features such as fever, rash, lymphadenopathy and evidence of other concurrent organ involvement).

4.9 Overdose

Symptoms most often accompanying modafinil overdose, alone or in combination with other medicinal products have included insomnia; central nervous system symptoms such as restlessness, disorientation, confusion, excitation, agitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Management
No specific antidote to the toxic effects of modafinil overdose has been identified to date. 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: centrally acting sympathomimetics
ATC Code: N06BA07

Modafinil promotes wakefulness in a variety of species, including man. The precise mechanism(s) through which modafinil promotes wakefulness is unknown.

In pre-clinical models, modafinil does not appear to be a direct or indirect acting $alpha_1$-adrenoceptor or dopamine receptor agonist. The wakefulness induced by amphetamine, but not by modafinil, is antagonised by the dopamine receptor antagonist haloperidol. Equal wakefulness-promoting doses of methylphenidate and amphetamine increase neuronal activation throughout the brain, but modafinil selectively and prominently increases neuronal activation in more discrete regions of the brain, especially in the hypothalamus.

In man, modafinil restores and/or improves the level and duration of wakefulness and daytime alertness in a dose-related manner. Administration of modafinil results in electrophysiological changes indicative of increased alertness and improvements in objective measures of ability to sustain wakefulness. Modafinil opposes the impairment of

cognitive, psychomotor and neurosensorial performances induced by sleep deprivation. These changes are produced without any adverse changes in behaviour and appetite.

In patients with narcolepsy, morning administration of 400 mg modafinil or administration of 200 mg modafinil in the morning and at noon does not adversely affect nocturnal sleep.

5.2 Pharmacokinetic properties

Modafinil is a racemic compound, whose enantiomers have different pharmacokinetics. The half-life of *l*-modafinil is approximately three times that of the *d* enantiomer, as is the total systemic exposure (AUC) to *l*-modafinil. Apparent steady state is reached after 2-4 days of dosing.

Absorption
Modafinil is readily absorbed, with peak plasma concentrations occurring at 2-4 hours. Food has no effect on overall modafinil bioavailability but t_{max} may be delayed by approximately one hour if modafinil is taken with food.

Distribution
Modafinil is well distributed in body tissue with an apparent volume of distribution larger than the volume of total body water. In human plasma, *in vitro*, modafinil is moderately bound to plasma protein (approximately 60%, mainly to albumin). This degree of protein binding is such that the risk of interaction with strongly bound substances is unlikely.

Biotransformation
Modafinil is metabolised in the liver to two major metabolites, modafinil acid and modafinil sulphone, by esterase enzymes and CYP3A4/5, respectively. In preclinical models, the metabolites did not appear to contribute to the arousal effects of modafinil. *In vitro* studies using human hepatocytes have demonstrated that modafinil slightly induces the following in a concentration-dependent manner: CYP1A2, CYP2B6 and CYP3A4. In addition, the activity of CYP2C9 was suppressed in the hepatocytes. In human liver microsomes, modafinil and modafinil sulphone produced partial competitive, reversible inhibition of CYP2C19 at concentrations expected during clinical use (see section 4.5).

Elimination
The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged (< 10%). The elimination half-life of modafinil after multiple doses is 15 hours and enables a treatment regimen based upon 1 or 2 doses per day.

Linearity/non-linearity
The pharmacokinetics of modafinil are linear and independent of the dose administered in the dose range of 200 to 600 mg once daily. Systemic exposure increases in proportion to doses administered.

Renal failure/hepatic impairment
In severe chronic renal failure the pharmacokinetics of modafinil were unaltered but exposure to modafinil acid was increased 9-fold (see section 4.2). There is minimal information available regarding the safety of such levels of this metabolite. In patients with severe hepatic impairment, oral clearance of modafinil was decreased by about 60% and the steady state concentration of modafinil was doubled. The dose of modafinil should be reduced by half in patients with severe hepatic or renal impairment (see section 4.2).

Elderly
Elderly patients may have diminished renal and/or hepatic function and dosage reductions should be considered (see section 4.2).

5.3 Preclinical safety data

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

Reproduction function studies have revealed no effect on fertility, nor any teratogenic effect, nor any effect on viability, growth or development of the offspring, although embryo resorptions, hydronephrosis and skeletal malformations have sometimes been associated with high dosages in rats.

Modafinil is not considered to be mutagenic or carcinogenic.

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

Microcrystalline cellulose
Pregelatinized maize starch
Sodium starch glycolate (Type A)
Povidone K 30
Silica, colloidal anhydrous
Sodium stearyl fumarate

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

Transparent PVC/PVdC aluminium blisters.
Blisters of 20, 30, 50, 60 and 90 tablets.
50 x 1 unit dose
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/18/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th September 2006

10 DATE OF REVISION OF THE TEXT

November 2008