Cephalon
deliver more>

27 FEB 2008
RECEIVED

Direct Healthcare Professional Communications on the association of Provigil® (Modafinil) with serious rash and psychiatric symptoms

25th February 2008

Dear Healthcare Professional,

In conjunction with EU regulatory authorities, including the Irish Medicines Board, Cephalon would like to inform you of the following new warnings and safety information for PROVIGIL® (modafinil) regarding serious skin rash and psychiatric symptoms which have been provided to the Irish Medicines Board in order to update the Irish Provigil SmPC. The product information will be updated accordingly.

Summary of the safety concern:

- **Serious skin rashes** requiring hospitalization and discontinuation of treatment have been reported in adults and children in association 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)].
  Modafinil should be discontinued at the first sign of rash and not restarted unless the rash is clearly not drug-related.

  You should instruct your patients that, if they develop any signs of a rash, they should discontinue the use of PROVIGIL and contact you immediately.

- **Psychiatric adverse experiences** (psychosis, mania, delusion, hallucinations, suicidal ideation and aggression) have been reported in patients treated with modafinil. If psychiatric symptoms occur, modafinil should be discontinued and not restarted.
  Caution should be exercised when administering modafinil to patients with a history of psychosis, depression or mania given the possible emergence or exacerbation of psychiatric symptoms.

Further information on the safety concern:

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, these rashes included 1 case of possible Stevens-Johnson Syndrome and one case of apparent multi-organ hypersensitivity), no serious skin rashes having been reported in adult clinical trials (0 per 4,264) of modafinil.

Serious cases of 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.

PROVIGIL is **not** approved for use in children for any indication.

PROVIGIL is indicated for the symptomatic relief of excessive sleepiness associated with narcolepsy, Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS) or moderate to severe chronic Shift Work Sleep Disorder (SWSD) in adult patients.

The revised SmPC for Provigil 100 mg and 200 mg tablets, including additional changes that were made recently, is attached in annex 1.

Prescribers are advised to report any suspected adverse reactions with Provigil to Cephalon Medical Information or the Irish Medicines Board in the usual way.

If you require any further information on Provigil please do not hesitate contacting us by phone on 01 2014000, by post or email InfoIRL@cephalon.com

ANNEX 1
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Provigil 100 mg Tablets
Provigil 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Modafinil 100 mg per tablet.
Modafinil 200 mg per tablet.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, capsule-shaped tablets, debossed with "PROVIGIL" on one side and "100 MG" on the other.
White to off-white, scored, capsule-shaped tablets, debossed with "PROVIGIL" on one side and "200 MG" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

PROVIGIL is indicated for the treatment of excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and moderate to severe chronic shift work sleep disorder.

4.2 Posology and method of administration

Adults
Narcolepsy and Obstructive Sleep Apnoea / Hypopnoea Syndrome
The recommended daily dose is 200-400 mg, commencing at 200 mg and titrated according to clinical response. PROVIGIL 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. Tablets should be swallowed whole.

For patients with obstructive sleep apnoea / hypopnoea syndrome, PROVIGIL treats the symptoms of excessive daytime sleepiness associated with the condition. In addition to this symptomatic treatment, disease-modifying interventions (e.g., Continuous Positive Airway Pressure) should be commenced or continued. Initiation of PROVIGIL treatment

should be by a physician experienced in the management of obstructive sleep apnoea / hypopnoea syndrome.

Moderate to Severe Chronic Shift Work Sleep Disorder
The recommended daily dose is 200 mg. PROVIGIL should be taken as a single dose approximately 1 hour prior to the start of the work shift. Tablets should be swallowed whole.

Elderly
There are limited data available on the use of PROVIGIL 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 per day).

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

4.3 Contra-indications

PROVIGIL is contra-indicated for use during pregnancy and lactation, or in patients with uncontrolled moderate to severe hypertension, or arrhythmia. PROVIGIL is also contra-indicated in patients with known hypersensitivity to PROVIGIL or any component of the preparation.

4.4 Special Warnings and Precautions for Use

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).

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

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.

Sexually active women of child-bearing potential should be established on a contraceptive programme before taking PROVIGIL (also see 4.5 with respect to potential interaction with oral contraceptives).

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

In patients with obstructive sleep apnoea / hypopnoea syndrome, the underlying condition and any associated cardiovascular pathology should be monitored.

Patients should be advised that PROVIGIL 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.

It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or cor pulmonale. PROVIGIL should not be used in patients with mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia.
Whilst studies with modafinil have demonstrated a low potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded.

PROVIGIL 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 Interactions 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 PROVIGIL 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 PROVIGIL.

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 ethinylestradiol should be taken or alternative/ concomitant methods of contraception should be considered. Adequate contraception will require continuation of the oral contraceptive for two cycles after stopping PROVIGIL.

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 PROVIGIL is administered concomitantly. Prothrombin times should be monitored regularly during the first 2 months of PROVIGIL use and after changes in PROVIGIL dosage.

Other drugs: Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol and omeprazole may have reduced clearance upon co-administration of PROVIGIL 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

There are no adequate data from the use of modafinil in pregnant women.

Modafinil was non-teratogenic in rats and rabbits at doses greater than the maximum clinical dose. However, plasma levels in preclinical studies, due to metabolic auto-induction, were less than or similar to that expected in patients.

Modafinil and its acid and sulphone metabolites pass into milk of lactating rats (see 5.3). It is not known whether modafinil passes into human milk.

Modafinil use during pregnancy and lactation is contra-indicated.

4.7 Effects on ability to drive and use Machines

There is no information available concerning the effects of PROVIGIL on vehicle driving and/or the ability to use machinery. Undesirable effects such as blurred vision or dizziness might affect ability to drive (see 4.8 Undesirable Effects).

4.8 Undesirable effects

The following undesired effects have been reported in clinical trials and/or post-marketing experience. The frequency of undesirable effects considered at least possibly related to treatment, in clinical trials involving 1561 patients taking PROVIGIL were as follows very common >1/10, common >1/100 to $\leq$ 1/10, uncommon >1/1000 to $\leq$ 1/100, unknown (cannot be estimated from 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.

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

Cardiac disorders
Common: tachycardia, palpitation.
Uncommon: extrasystoles, arrhythmia, bradycardia,

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

Blood and lymphatic system disorders
Uncommon: eosinophilia, leucopenia

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

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

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.

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

Infections and infestations
Uncommon: pharyngitis, sinusitis

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)

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

Renal and urinary disorders
Uncommon: abnormal urine, urinary frequency

Vascular disorders:
Common: vasodilatation
Uncommon: hypertension, hypotension

General disorders and administration site conditions
Common: asthenia, chest pain
Uncommon: peripheral oedema, thirst

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).

Reproductive system and breast disorders
Uncommon: menstrual disorder

Psychiatric disorders
Common: nervousness, insomnia, anxiety, depression, abnormal thinking, confusion
Uncommon: sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, agitation, abnormal dreams, aggression
Unknown: psychosis, mania, delusions, hallucinations and suicidal ideation

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

Therapeutic class: centrally acting sympathomimetic (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 amfetamine, but not by modafinil, is antagonised by the dopamine receptor antagonist haloperidol. Equal wakefulness-promoting doses of methylphenidate and amfetamine 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 performance 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 PROVIGIL 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 drugs 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 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 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 PROVIGIL should be reduced by half in patients with severe hepatic or renal impairment (see 4.2).

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

Modafinil is not considered to be mutagenic or carcinogenic.

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
Pregelatinised starch
Microcrystalline cellulose
Croscarmellose sodium
Povidone K29/32
Magnesium stearate

6.2 Incompatibilities

Not Application

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

No special precautions for storage.

6.5 Nature and Contents of Container

Opaque PVC/PVDC/Aluminium blisters containing 10 tablets

Packs containing 30, 60 or 90 tablets.

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

Not applicable

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
11/13 Frederick Sanger Road
Surrey Research Park
Guildford
Surrey GU2 7YD
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 827/1/1
PA 827/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

PA 827/1/1 – 1 May 1998 / 1 May 2003
PA 827/1/2 – 19 September 2003

10 DATE OF REVISION OF THE TEXT

February 2008