SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

Modafinil 100 iPharma, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Modafinil 100 iPharma: Each tablet contains 100 mg modafinil.

Excipient with known effect:

Contains sugar (49,4 mg lactose monohydrate per tablet)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

White, circular, biconvex tablet and without irregularities, 9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Modafinil 100 iPharma is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, as defined by either of the two following DSM IV criteria in the absence of other clinically significant medical or psychotic conditions:

1. Recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), or
2. a Complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviours, disrupted major sleep episodes; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes.

The effectiveness of Modafinil iPharma has not been evaluated in placebo-controlled studies of more than 9 weeks.

4.2 Posology and method of administration

Posology

ADULTS: The dose of Modafinil iPharma is 200 mg/day, given as a single dose in the morning. Doses of 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose.

ELDERLY: In elderly patients, elimination of Modafinil iPharma and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses in this population.

Hepatic failure

The dose in patients with hepatic failure should be reduced by half (100-200 mg/day).

Paediatric population

Modafinil iPharma should not be used in children aged less than 16 years old because of safety and efficacy concerns (see sections 4.3 and 4.4).

4.3 Contraindications

- Hypersensitivity to modafinil, or to any of the excipients listed in section 6.1
- Major anxiety (outside specialised units).
- Children and adolescents under the age of 16 years.
- Severe renal impairment.
- Uncontrolled moderate to severe hypertension.
- Cardiac dysrhythmias.

4.4 Special warnings and precautions for use

Diagnosis of sleep disorders

Modafinil iPharma 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 iPharma 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 iPharma is not recommended in the paediatric population (below 16 years).

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 iPharma.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalisation 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 iPharma 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 iPharma should be

discontinued and not restarted. Caution should be exercised in giving Modafinil iPharma to patients with a history of psychiatric disorders including psychosis, depression, mania, major anxiety, agitation, insomnia or substance abuse (see below).

One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of Modafinil iPharma and sleep deprivation. There was no evidence of psychosis 36 hours after medicine discontinuation. Caution should be exercised when Modafinil iPharma is given to patients with a history of psychosis.

Anxiety

Modafinil iPharma is associated with the onset or worsening of anxiety. Patients with major anxiety should only receive treatment with Modafinil iPharma 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 iPharma should be carefully monitored for the appearance or worsening of suicide related behaviour. If suicide-related symptoms develop in association with Modafinil iPharma, 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 iPharma should be carefully monitored for the appearance or worsening of psychotic or manic symptoms. If psychotic or manic symptoms occur, discontinuation of Modafinil iPharma may be required.

Bipolar disorders

Care should be taken in using Modafinil iPharma 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 iPharma. Patients treated with Modafinil iPharma should be carefully monitored for the appearance or worsening of aggressive or hostile behaviour. If symptoms occur, discontinuation of Modafinil iPharma may be required.

Cardiovascular risks

An ECG is recommended in all patients before Modafinil iPharma treatment is initiated. Patients with abnormal findings should receive further specialist evaluation and treatment before Modafinil iPharma treatment is considered.

Blood pressure and heart rate should be regularly monitored in patients receiving Modafinil iPharma. Modafinil iPharma should be discontinued in patients who develop dysrhythmia or moderate to severe hypertension and not restarted until the condition has been adequately evaluated and treated.

Modafinil iPharma 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 dysrhythmia.

Modafinil iPharma has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution.

Modafinil iPharma has not been systematically evaluated in patients with hypertension. Periodic monitoring of hypertensive patients may be appropriate.

Insomnia

Because Modafinil iPharma promotes wakefulness, caution should be paid to signs of insomnia.

Maintenance of sleep hygiene

Patients should be advised that Modafinil iPharma 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 iPharma. 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 iPharma (also see section 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 iPharma to patients with history of alcohol, drug or illicit substance abuse.

Patients with severe renal impairment

In patients with severe renal impairment (mean creatinine clearance = 16,6 ml/min), a 200 mg single dose of Modafinil iPharma did not lead to increased exposure to modafinil but resulted in much higher exposure to the inactive metabolite, modafinil acid, than is seen in subjects with normal renal function. There is little information available about the safety of such levels of this metabolite (see section 5.2).

Patients with severe hepatic impairment

In patients with severe hepatic impairment, with or without cirrhosis (see section 5.2) Modafinil iPharma should be administered at a reduced dose as the clearance of modafinil was decreased compared to that in normal subjects (see section 4.2).

Elderly patients

To the extent that elderly patients may have diminished renal and/or hepatic function, dosage reductions should be considered (see section 4.2).

Lactose intolerance

Modafinil iPharma contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Modafinil iPharma.

4.5 Interaction with other medicines 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.

Chronic dosing of Modafinil iPharma at 400 mg/day once daily resulted in a ~20 % mean decrease in modafinil plasma trough concentrations by week 9, relative to those at week 3, suggesting that chronic administration of Modafinil iPharma might have caused induction of its metabolism.

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 iPharma.

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 iPharma. Adequate contraception will require continuation of these methods for two months after stopping Modafinil iPharma.

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 iPharma use and after changes in modafinil dosage.

Other medicines

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 medicines 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 pre-systemic 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

Women of childbearing potential / Contraception in males and females

Women of childbearing potential have to use effective contraception. As Modafinil iPharma may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see section 4.4 and 4.5). Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with Modafinil iPharma tablets and for one month after discontinuation of therapy.

Pregnancy

Safety in pregnancy has not been established.

Based on 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).

Modafinil iPharma should not be used during pregnancy.

Lactation

Safety in lactation has not been established.

Available pharmacodynamic/toxicological data in animals have shown excretion of modafinil/metabolites in milk (for details see section 5.3).

Modafinil iPharma should not be used during breastfeeding.

Fertility

No data on fertility are available in humans. At exposures similar to human levels at the recommended human dose, modafinil slightly increased the time to mate in female rats. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

4.7 Effects on ability to drive and use machines

Patients with abnormal levels of sleepiness who take Modafinil iPharma should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking Modafinil iPharma 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).

Patients should be cautioned about operating a vehicle or other hazardous machinery until they are reasonably certain that Modafinil iPharma therapy will not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reaction is headache.

Tabulated list of adverse reactions:

MedDRA System Organ Class	
Infections and infestations	
Less frequent	Pharyngitis, sinusitis
Frequency unknown	Infection, flu syndrome, fever/chills, hypothermia
Blood and lymphatic system disorders	
Less frequent	Eosinophilia, leukopenia
Frequency unknown	Anaemia, leucocytosis
Immune system disorders	
Less frequent	Minor allergic reaction (e.g., hay fever symptoms)
Frequency unknown	Angioedema, urticaria (hives), hypersensitivity reactions (characterised by features such as fever, rash, lymphadenopathy and evidence of other concurrent organ involvement), anaphylaxis
Metabolic and nutrition disorders	
Frequent	Decreased appetite
Less frequent	Hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite, albuminuria
Psychiatric disorders	
Frequent	Nervousness, insomnia, anxiety, depression, abnormal thinking, confusion, irritability
Less frequent	Sleep disorder, emotional lability, decreased libido, hostility, depersonalisation, personality disorder, abnormal dreams, agitation, aggression, suicidal ideation, psychomotor hyperactivity, hallucinations, mania, psychosis
Frequency unknown	Delusions
Nervous system disorders	
Frequent	Headache, dizziness, somnolence, paraesthesia
Less frequent	Dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion
Frequency unknown	Cataplexy
Eye disorders	
Frequent	Blurred vision
Less frequent	Abnormal vision, dry eye, amblyopia
Ear and labyrinth disorders	

Frequency unknown	Ear pain, ear disorders
Cardiac disorders	
Frequent	Tachycardia, palpitation
Less frequent	Extrasystoles, dysrhythmia, bradycardia
Vascular disorders	
Frequent	Vasodilatation
Less frequent	Hypertension, hypotension, syncope
Respiratory, thoracic and mediastinal disorders	
Less frequent	Dyspnoea, increased cough, asthma, epistaxis, rhinitis
Frequency unknown	Bronchitis, pneumonia
Gastrointestinal disorders	
Frequent	Abdominal pain, nausea, dry mouth, diarrhoea, dyspepsia, constipation
Less frequent	Flatulence, reflux, vomiting, dysphagia, glossitis, mouth ulcers
Frequency unknown	Tooth disorders, vomiting, gingivitis, anorexia
Skin and subcutaneous tissue disorders	
Less frequent	Sweating, rash, acne, pruritus
Frequency unknown	Serious skin reactions, including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), psoriasis, ecchymosis, dry skin
Musculoskeletal and connective tissue disorders	
Less frequent	Back pain, neck pain, myalgia, myasthenia, leg cramps, arthralgia, twitch
Renal and urinary disorders	
Less frequent	Abnormal urine, urinary frequency, abnormal ejaculation
Frequency unknown	Urinary tract infections, pyuria, haematuria, cystitis
Reproductive system and breast disorders	
Less frequent	Menstrual disorder
Frequency unknown	Dysmenorrhoea
General disorders and administration site conditions	
Frequent	Asthenia, chest pain
Less frequent	Peripheral oedema, thirst
Investigations	
Frequent	Abnormal liver function tests, dose related increases in alkaline phosphatase and gamma-glutamyl transferase have been observed.
Less frequent	Abnormal ECG, weight increase, weight decrease
Frequency unknown	Increased AST
Injury, poisoning and procedural complications	
Frequency unknown	Accidental injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Death has occurred with Modafinil iPharma overdose alone or in combination with other medicines. 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, agitation, anxiety, excitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain.

Management

Induced emesis 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

Category and Class: A 1.1 Central analeptics

Pharmacotherapeutic group: Psychoanaleptics, centrally acting sympathomimetics, ATC code: N06BA07.

Mechanism of action

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

Pharmacodynamic effects

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 (noradrenaline), 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 α_1-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 α_1-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.

5.2 Pharmacokinetic properties

Modafinil is a racemic compound, and the enantiomers have different pharmacokinetics where the elimination $t_{½}$ of the R-isomer is three times that of the S-isomer in adult humans.

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 (t_{max}) may be delayed by approximately one hour if taken with food.

Distribution

Modafinil is well distributed in body tissue with an apparent volume of distribution (~0,9 l/kg) larger than the volume of total body water (0,6 l/kg). 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 medicines.

At serum concentrations obtained at steady state after doses of 200 mg/day, modafinil exhibits no displacement of protein binding of warfarin, diazepam, or propranolol. Even at much larger concentrations (1000 µM; >25 times the C_{max} of 40 µM at steady state at 400 mg/day), modafinil has no effect on warfarin binding. Modafinil acid at concentrations >500 µM decreases the extent of warfarin binding, but these concentrations are >35 times those achieved therapeutically.

Biotransformation

Modafinil is metabolised by the liver. The chief metabolite (40 – 50 % of the dose), modafinil acid, has no pharmacological activity. Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation, and glucuronide conjugation. Less than 10 % of an administered dose is excreted as the parent compound.

In humans, modafinil shows a possible induction effect on its own metabolism after chronic administration of doses >400 mg/day. Induction of hepatic metabolising enzymes, most importantly cytochrome P-450 (CYP) 3A4, has also been observed *in vitro* after incubation of primary cultures of human hepatocytes with modafinil.

Elimination

The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged (<10 % of the dose). Urine alkalinisation has no effect on the elimination of modafinil.

The effective elimination half-life of modafinil after multiple doses is about 15 hours.

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.

Special populations

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

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential. However, modafinil plasma exposure in animals was generally less than or similar to that expected in humans.

At exposures similar to human levels at the recommended human dose, modafinil slightly increased the time to mate in female rats, and induced embryo-toxic, but no teratogenic effects in two species (rats and rabbits). In the rat peri-postnatal study, the number of dams with stillborn pups was slightly increased at exposures below human levels, but postnatal development was otherwise not adversely affected at exposures similar to human levels. Modafinil concentration in milk was about 11,5 times higher than in plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Povidone K29/32, Pregelatinised starch (maize), Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging until required for use.

6.5 Nature and contents of container

Modafinil 100 iPharma tablets are packed in heat-sealed PVC – Aluminium blister packs.

Blister strips of Modafinil 100 iPharma tablets are packed together with the leaflets in cardboards cartons of 30 tablets.

6.6 Special precautions for disposal and other handling

No special precautions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

49/1.1/0260

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2021

10 DATE OF REVISION OF THE TEXT

16 November 2021