PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF MEDICINE

PROLERT® 100, tablets

PROLERT® 200, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg or 200 mg of modafinil.

Excipient(s) with known effect:

Contains sugar (lactose).

Each 100 mg tablet contains 104 mg lactose.

Each 200 mg tablet contains 208 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

PROLERT 100: The product is presented as a white to off-white capsule shaped tablet embossed with ‘100’, containing 100 mg of modafinil.

PROLERT 200: The product is presented as a white to off-white capsule shaped tablet embossed with ‘200’, containing 200 mg of modafinil.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROLERT is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, as defined by either of the two following DSM IV (Diagnostic and statistical manual of mental disorders) 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 hallucination, 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 as in PROLERT 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 PROLERT is 200 mg per day, given as a single dose in the morning.

Doses of 400 mg per day, given as a single dose, have been well tolerated. There is however no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose.

Elderly patients (65 years and older)

Elimination of modafinil and its metabolites may be reduced as a consequence of aging. It should therefore be considered to reduce the dose in elderly patients.

Hepatic failure

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

Paediatric population

PROLERT should not be used in children below 16 years of age because of safety and efficacy concerns (see section 4.3).

Method of administration

For oral use. Tablets should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to modafinil or to any of the excipients of PROLERT 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.
- In patients with cardiac dysrhythmias.

4.4 Special warnings and precautions for use

Diagnosis of sleep disorders

PROLERT should be used only in patients who have had a complete evaluation of their excessive sleepiness. 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 SJS (Stevens-Johnson syndrome), TEN (toxic epidermal necrolysis) and DRESS (drug rash with eosinophilia and systemic symptoms)

Serious rash, requiring hospitalisation and discontinuation of treatment has been reported with the use of PROLERT occurring within 1 to 5 weeks after treatment initiation. Cases have also been reported after prolonged treatment (e.g., 3 months).

PROLERT should be discontinued at the first sign of rash and not restarted (see section 4.8).

Rare cases of serious or life-threatening rash, including SJS, TEN and DRESS have been reported in worldwide post-marketing experience.

Patients should be advised to notify their doctor if they develop a rash, hives, or a related allergic phenomenon.

Paediatric population

Because safety and effectiveness in controlled studies in children (below 16 years) have not been established and because of the risk of serious cutaneous hypersensitivity and psychiatric adverse reactions, the use of PROLERT is not recommended in this population (see section 4.3).

Multi-organ hypersensitivity reaction

Multi-organ hypersensitivity reactions, including fatal reactions, have occurred in close temporal association to the initiation of modafinil (contained in PROLERT).

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, PROLERT should be discontinued.

Psychiatric disorders

Patients should be monitored for the development of new, 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 PROLERT treatment, PROLERT should be discontinued and not restarted. Caution should be exercised in giving PROLERT to patients with a history of psychiatric disorders including psychosis, depression, mania, major anxiety, agitation, insomnia or substance abuse (see below).

Anxiety

Modafinil (contained in PROLERT) is associated with the onset or worsening of anxiety. Periodic specialist clinical assessment is necessary. 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 (contained in PROLERT). Patients treated with PROLERT should be carefully monitored for the appearance or worsening of suicide-related behaviour. If suicide-related symptoms develop in association with PROLERT, treatment should be discontinued.

Psychotic or manic symptoms

Modafinil (contained in PROLERT) is associated with the onset or worsening of psychotic symptoms or manic symptoms (including hallucinations, delusions, agitation or mania). Patients treated with PROLERT should be carefully monitored for the appearance or worsening of psychotic or manic symptoms. If psychotic or manic symptoms occur, discontinuation of PROLERT may be required.

Bipolar disorders

Care should be taken in using PROLERT 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 PROLERT. Patients treated with PROLERT should be carefully monitored for the appearance or worsening of

aggressive or hostile behaviour. If symptoms occur, discontinuation of PROLERT may be required.

Cardiovascular risks

An electrocardiogram (ECG) is recommended in all patients before PROLERT treatment is initiated. Patients with abnormal findings should receive further specialist evaluation and treatment before PROLERT treatment is considered.

Blood pressure and heart rate should be regularly monitored in patients receiving PROLERT. PROLERT 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.

It is recommended that PROLERT tablets not be used 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 central nervous system (CNS) stimulants. This syndrome may present with ischaemic ECG changes, chest pain or dysrhythmia.

Insomnia

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

Maintenance of sleep hygiene

Patients should be advised that PROLERT 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.

Abuse, misuse, diversion

The potential for dependence with long-term use exists.

Caution should be exercised in administering PROLERT to patients with history of alcohol, medicine or illicit substance abuse.

Patients using steroidal contraceptives

Sexually active women of childbearing potential should be established on a contraceptive programme before taking PROLERT. Since the effectiveness of steroidal contraceptives may be reduced when used with PROLERT, alternative or concomitant methods of contraception are recommended, and for two months after discontinuation of PROLERT. See section 4.5 with respect to potential interaction with steroidal contraceptives.

Patients with severe renal impairment

PROLERT is contraindicated in severe renal impairment (mean creatinine clearance = 16,6 ml/min). See section 4.3.

In patients with severe renal impairment, a 200 mg single dose of modafinil as in PROLERT 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 5.1) PROLERT should be administered at a reduced dose as the clearance of modafinil was decreased compared to that in normal persons (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

PROLERT contains lactose (see section 2).

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

4.5 Interaction with other medicines and other forms of interaction

Modafinil (contained in PROLERT) 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 cytochrome P450 enzymes (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 PROLERT 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 PROLERT.

Steroidal contraceptives:

The effectiveness of steroidal contraceptives may be impaired due to induction of CYP3A4/5 by modafinil (contained in PROLERT). Alternative or concomitant methods of contraception are recommended for patients treated with PROLERT, when oral contraceptives are used, a product containing 50 micrograms or more of ethinyl estradiol should be taken. Adequate contraception will require continuation of these methods for two months after stopping PROLERT.

Antidepressants:

A number of tricyclic antidepressants, e.g. clomipramine, desipramine 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 (contained in PROLERT) the clearance of warfarin may be decreased when modafinil is administered concomitantly. Prothrombin times should be monitored regularly during the first 2 months of PROLERT use and after changes in PROLERT 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 PROLERT 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 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 PROLERT was initiated.

Co-administration of potent inducers of CYP3A4 (e.g. rifampicin) or inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole) could alter the

levels of modafinil due to the partial involvement of that enzyme in the metabolic elimination of the compound.

As PROLERT causes a modest induction of CYP3A4 the clearance of theophylline, a CYP3A4 substrate, may be increased.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity.

Safety in pregnancy has not been established.

PROLERT should not be used during pregnancy.

Patients should be advised to inform their doctor if they become pregnant or intend to become pregnant during therapy.

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 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 PROLERT and for two months after discontinuation of therapy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of modafinil/metabolites in milk.

Safety during breastfeeding has not been established.

PROLERT should not be used during breast feeding.

Fertility

No data on fertility are available in humans.

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

The most frequently reported adverse reaction is headache, affecting approximately 21 % of patients. This is usually mild or moderate, dose-dependent and disappears within a few days.

Tabulated summary of adverse reactions

System organ class	Adverse reaction
Infections and infestations	
Less frequent:	pharyngitis, sinusitis
Blood and lymphatic system disorders	
Less frequent:	eosinophilia, leukopenia
Immune system disorders	
Less frequent:	minor allergic reaction (e.g., hay fever symptoms)
Not known:	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	
Frequent:	decreased appetite, anorexia
Less frequent:	hypercholesterolaemia, hyperglycaemia, diabetes mellitus, increased appetite
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
Not known:	delusions
Nervous system disorders	
Frequent:	headache, dizziness, somnolence, paraesthesia, cataplexy, ataxia
Less frequent:	dyskinesia, hypertonia, hyperkinesia, amnesia, migraine, tremor, vertigo, CNS stimulation, hypoaesthesia, incoordination, movement disorder, speech disorder, taste perversion
Eye disorders	
Frequent:	blurred vision, amblyopia
Less frequent:	abnormal vision, dry eye
Cardiac disorders	
Frequent:	tachycardia, palpitation
Less frequent:	extrasystoles, dysrhythmia, bradycardia, abnormal ECG
Vascular disorders	
Frequent:	vasodilatation, syncope
Less frequent:	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	
Frequent:	lung disorders

Less frequent:	dyspnoea, increased cough, asthma, epistaxis, rhinitis
Gastrointestinal disorders	
Frequent:	abdominal pain, nausea, dry mouth, diarrhoea, dyspepsia, constipation, gingivitis
Less frequent:	flatulence, reflux, vomiting, dysphagia, glossitis, mouth ulcers
Skin and subcutaneous tissue disorders	
Frequent:	herpes simplex, dry skin
Less frequent:	sweating, rash, acne, pruritus
Not known:	serious skin reactions, including erythema multiforme, SJS, TEN and DRESS
Musculoskeletal and connective tissue disorders	
Frequent:	joint disorders
Less frequent:	back pain, neck pain, myalgia, myasthenia, leg cramps, arthralgia, twitch
Renal and urinary disorders	
Frequent:	albuminuria, urinary retention
Less frequent:	abnormal urine, urinary frequency
Reproductive system and breast disorders	
Frequent:	abnormal ejaculation
Less frequent:	menstrual disorder

General disorders and administration site conditions	
Frequent:	asthenia, chest pain, chills, rigid neck, fever
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:	weight increase, weight decrease
Not known:	positive test for detection of drug abuse

Drug abuse and dependence

In addition to its wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROLERT produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. Modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release.

Results reported from a clinical study that assessed the abuse potential of modafinil relative to methylphenidate, demonstrated that modafinil produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate).

Doctors should follow patients closely, especially those with a history of drug and/or stimulant (e.g. methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g.

incrementation of doses or drug-seeking behaviour). See section 4.4 “Abuse, misuse, diversion”.

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

In overdose, side effects can be precipitated and/or be of increased severity, see section 4.8. Death has occurred with modafinil overdose alone or in combination with other medicines.

Symptoms most often accompanying modafinil overdose, alone or in combination with other medicines 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 may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.1 Central analeptics

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

The mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like sympathomimetic medicines including amphetamine and methylphenidate, although the pharmacological profile is not identical to that of sympathomimetic amines.

At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V.

Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several *in vivo* pre-clinical models capable of detecting enhanced dopaminergic activity. *In vitro,* modafinil binds to the

dopamine reuptake site and causes an increase in extra-cellular dopamine, but no increase in dopamine release. In a pre-clinical model, the wakefulness induced by amphetamine, but not modafinil, is antagonised by the dopamine receptor antagonist haloperidol.

Modafinil does not appear to be a direct or indirect α1-adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin, in assay systems known to be responsive to α-adrenergic agonists, modafinil has no activity. Modafinil does not display sympathomimetic activity in the rat vas deferens preparations (agonist-stimulated or electrically stimulated) nor does it increase the formation of the adrenergic receptor-mediated second messenger phosphatidyl inositol in *in vitro* models. Unlike sympathomimetic medicines, modafinil does not reduce cataplexy in narcoleptic canines and has minimal effects on cardiovascular and haemodynamic parameters.

In addition to its wakefulness-promoting effects and increased locomotor activity in animals, in humans, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.

5.2 Pharmacokinetic properties

Modafinil is a racemic compound, and the enantiomers have different pharmacokinetics (e.g. half-life of the *l*-isomer is about three times that

of the *d*-isomer in humans). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration (C_{minss}) of circulating modafinil after once daily dosing consists of 90 % of the *l*-isomer and 10 % of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers of modafinil exhibit linear kinetics upon multiple dosing of 200 to 600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2 to 4 days of dosing.

Absorption

Modafinil is well-absorbed with peak plasma concentrations occurring at 2 to 4 hours after administration.

The bioavailability of PROLERT tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined due to the aqueous insolubility (< 1 mg/ml) of modafinil, which precluded intravenous 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 human plasma protein (approximately 60 %, mainly to albumin).

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 (1 000 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

Metabolism occurs through hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation and glucuronide conjugation.

The major route of elimination (about 90 %) is metabolism, mainly by the liver, with subsequent renal elimination of the metabolites. Urine alkalinisation has no effect on the elimination of modafinil.

The largest fraction of modafinil in the urine is modafinil acid, but at least six other metabolites are present in lower concentrations. Only two metabolites reach appreciable concentrations in plasma, namely modafinil acid and modafinil sulfone. In pre-clinical models modafinil acid, modafinil sulfone, 2-[(diphenylmethyl)sulfonyl]acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil.

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 (see section 4.5 for further information on interactions).

Elimination

The excretion of modafinil and its metabolites is chiefly renal, with a small proportion being eliminated unchanged as the parent compound (< 10 % of the dose).

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

Special populations

Gender

The pharmacokinetics of modafinil is not affected by gender.

Elderly population

There are limited data available on the use of modafinil in elderly patients. The potential for lower clearance and increased systemic exposure should be kept in mind when treating this population (see section 4.2). 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.

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 (see section 4.4).

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 normal patients. The dosage of modafinil (as in PROLERT) should be reduced in patients with severe hepatic impairment (see sections 4.4 and 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Crospovidone

Povidone K30

Lactose anhydrous

Talc

Colloidal anhydrous silica

Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months at or below 25 °C.

6.4 Special precautions for storage

PROLERT does not require any special storage conditions. Keep blisters in cartons.

6.5 Nature and contents of container

PROLERT 100 & 200 tablets are packed in blisters of PVC/PE/PCTFE 191/70/51 white opaque laminate with 20 micron aluminium lidding foil

blisters or in PVC/PVDC 250/60 white opaque laminate with 20 micron aluminium lidding foil blisters. Batch number and Expiry date are overprinted/embossed on the blister.

The blister strips are packed in outer carton boxes. Each carton contains 10, 20, 30, 60, 90 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

South Africa

8. REGISTRATION NUMBERS

PROLERT 100: 52/1.1/0812

PROLERT 200: 52/1.1/0813

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 February 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.