PROFESSIONAL INFORMATION FOR PHENITAB

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

PHENITAB 18 extended release tablets

PHENITAB 27 extended release tablets

PHENITAB 36 extended release tablets

PHENITAB 54 extended release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PHENITAB 18: Each extended release tablet contains 18 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate, 40 mg).

PHENITAB 27: Each extended release tablet contains 27 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate, 40 mg).

PHENITAB 36: Each extended release tablet contains 36 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate, 40 mg).

PHENITAB 54: Each extended release tablet contains 54 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate, 40 mg).

For full list of excipients, see section 6.1

PROFESSIONAL INFORMATION FOR PHENITAB

3. PHARMACEUTICAL FORM

Extended release tablets

PHENITAB 18: round, biconvex, yellow and homogeneous aspect film-coated tablets of approximately 8,5 mm of diameter with a hole in one side of the tablet.

PHENITAB 27: round, biconvex, grey and homogeneous aspect film-coated tablets of approximately 8,5 mm of diameter with a hole in one side of the tablet.

PHENITAB 36: round, biconvex, white and homogeneous aspect film-coated tablets of approximately 10 mm of diameter with a hole in one side of the tablet.

PHENITAB 54: round, biconvex, pink and homogeneous aspect film-coated tablets of approximately 10 mm of diameter with a hole in one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHENITAB is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6 – 17 and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

4.2 Posology and method of administration

Posology

Dosage should be individualised according to the need and response of each individual patient.

Patients new to methylphenidate:

The recommended starting dose of **PHENITAB** tor patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults.

Patients currently using methylphenidate:

The recommended dose of **PHENITAB** for patients who are currently taking methylphenidate three times daily at doses of 15 to 60 mg/day is provided in Table 2. Dosing recommendations are based on current dose regimen and clinical judgement.

Table 2. Recommended Dose Conversion from Other Methylphenidate Regimens to **PHENITAB**

Previous Methylphenidate Daily Dose	**Recommended PHENITAB Dose**
5 mg Methylphenidate hydrochloride twice daily or three times daily	18 mg once daily
10 mg Methylphenidate hydrochloride twice daily or three times daily	36 mg once daily
15 mg Methylphenidate hydrochloride twice daily or three times daily	54 mg once daily
20 mg Methylphenidate hydrochloride twice daily or three times daily	72 mg once daily

Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate in other regimens.

Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day for children aged between 6 – 12 years and to a maximum of 72 mg for adolescents aged between 13 – 18 years and 108 mg in adults. In general, dosage adjustment may proceed at approximately weekly intervals. Daily dosage above 54 mg is not recommended in children aged between 6 – 12 years. Daily dosage above 72 mg is not recommended in adolescents aged between 13 – 18 years. Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended Treatment:

The long-term use of **PHENITAB** has not been systemically evaluated in controlled clinical trials. The medical practitioner who elects to use **PHENITAB** for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the medicine for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.

Dose reduction and discontinuation:

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, **PHENITAB** should be discontinued.

Special populations

Elderly:

Use of **PHENITAB** in elderly patients over 65 years has not been studied in controlled trials.

Paediatric population:

PHENITAB should not be used in patients under six years old.

Method of administration:

PHENITAB is administered orally once daily. As the effect has been shown to be present 12 hours after dosing, the product should be taken in the morning.

PHENITAB should be swallowed whole with adequate amounts of liquids, and must not be chewed, divided, or crushed.

PHENITAB may be administered with or without food.

4.3 Contraindications

PHENITAB is contraindicated:

- In patients known to be hypersensitive to methylphenidate or other components

of **PHENITAB** (see section 6.1)

- In patients with marked anxiety, tension, and agitation, since **PHENITAB** may aggravate these symptoms
- In patients with glaucoma
- In patients with a family history or diagnosis of Tourette's Syndrome
- During treatment with monoamine oxidase inhibitors, and within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (as hypertensive crises may result).
- Phaeochromocytoma
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke
- In pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

PHENITAB treatment is not indicated in all children with ADHD and the decision to use the medicine must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and not simply on the presence of one or more abnormal behavioural characteristics.

PHENITAB should not be used for the treatment of attention deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long-term use of methylphenidate, as in **PHENITAB**, has not been systematically evaluated in controlled trials. **PHENITAB** treatment should not and need not, be indefinite. **PHENITAB** treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The medical practitioner who elects to use **PHENITAB** for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the medicine for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that **PHENITAB** is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

Use in adults

Safety and efficacy have not been established for the initiation of treatment in adults or the routine continuation of treatment beyond 18 years of age. If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these

adults should be reviewed regularly and undertaken annually.

Use in the elderly

PHENITAB should not be used in the elderly as ~~S~~safety and efficacy have not been established in this age group.

Use in children under 6 years of age

PHENITAB should not be used in patients under six years old. Sufficient data on the safety of long-term use of **PHENITAB** is not yet available.

Cardiovascular status

Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant dysrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during **PHENITAB** treatment should undergo a prompt specialist cardiac evaluation.

PHENITAB increases heart rate, systolic and diastolic blood pressure, therefore caution is advised when **PHENITAB** is prescribed for ADHD patients whose underlying medical conditions might be compromised by increases in heart rate and/or blood pressure e.g. heart failure and hypertension. Blood pressure should be monitored in patients treated with **PHENITAB** especially those with hypertension (see section 4.3).

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate, as in **PHENITAB**, is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric cardiac advice has been obtained (see section 4.3).

Sudden death and pre-existing structural cardiac abnormalities or other serious cardiac disorders:

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Caution is advised when **PHENITAB**, is prescribed for ADHD patients with structural cardiac abnormalities.

Misuse and cardiovascular events

Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders

See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with **PHENITAB**.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of **PHENITAB** and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during **PHENITAB** therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with **PHENITAB** is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products, including **PHENITAB**. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, **PHENITAB** should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms

In psychotic patients, administration of methylphenidate, as in **PHENITAB**, may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and

delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate, as in **PHENITAB**, at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for **PHENITAB**, and discontinuation of treatment may be appropriate. Caution is advised.

Aggressive or hostile behaviour

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Aggression has been reported in patients treated with methylphenidate (see section 4.8). Patients treated with methylphenidate, as in **PHENITAB**, should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Doctors should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their doctor. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of **PHENITAB**.

Tics

PHENITAB has been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of **PHENITAB**. Patients should be regularly monitored for the emergence or worsening of tics during treatment with **PHENITAB.** Monitoring should be at every

adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension

Anxiety, agitation and tension have been reported in patients treated with methylphenidate, as in **PHENITAB** (see section 4.8). Methylphenidate is also associated with the worsening of pre-existing anxiety, agitation or tension, and anxiety led to discontinuation of methylphenidate in some patients. Clinical evaluation for anxiety, agitation or tension should precede use of **PHENITAB** and patients should be regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.

Forms of bipolar disorder

Particular care should be taken in using **PHENITAB** to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with **PHENITAB**, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close ongoing monitoring is essential in these patients (see above **'Psychiatric Disorders'**). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Growth

Although a causal relationship has not been established, suppression of growth (i.e. weight gain, and/or height) has been reported with the long-term use of **PHENITAB** in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Seizures

PHENITAB should be used with caution in patients with epilepsy. Methylphenidate, as in **PHENITAB**, may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and less frequently in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, **PHENITAB** should be discontinued.

Priapism

Prolonged and painful erections have been reported in association with methylphenidate products, as in **PHENITAB**, mainly in association with a change in the treatment regimen. Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Use with serotonergic medicines

Serotonin syndrome has been reported following coadministration of methylphenidate with serotonergic medicines. If concomitant use of **PHENITAB** with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). **PHENITAB** must be discontinued as soon as possible if serotonin syndrome is suspected and appropriate treatment instituted.

Abuse, misuse and diversion

Patients should be carefully monitored for the risk of diversion, misuse and abuse of **PHENITAB**.

PHENITAB should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion. Chronic abuse of **PHENITAB** can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse. Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative. For some high-risk substance abuse patients, **PHENITAB** or other stimulants may not be suitable and nonstimulant treatment should be considered.

Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic overactivity. Some patients may require long-term follow up. Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Depression/Fatigue

PHENITAB should not be used to treat depression and/or for the prevention or treatment of normal fatigue states.

Interference with serological testing

PHENITAB contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency

There is no experience with the use of methylphenidate, as in **PHENITAB**, in patients

with renal or hepatic insufficiency.

Haematological effects

The long-term safety of treatment with methylphenidate is not fully known.

Periodic haematologic monitoring (complete blood count, differential, and platelet counts) is advised during prolonged therapy. In the event of leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction

PHENITAB must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided or crushed. Methylphenidate is contained within a non-absorbable shell designed to release the medicine at an extended rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stools something that looks like a tablet.

Because the **PHENITAB** tablet is non-deformable and does not appreciably change in shape in the GI tract, **PHENITAB** should not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been reports of obstructive symptoms in patients with known strictures. Due to the extended release design of the tablet, **PHENITAB** should only be used in patients who are able to swallow the tablet whole.

Visual

Symptoms of visual disturbances have been reported. Difficulties with accommodation and blurring of vision have been reported.

Excipient warning:

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

PHENITAB contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended when ~~at~~ combining **PHENITAB** with other medicines, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with **PHENITAB**, it may be necessary to adjust the dosage of these medicines already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive medicines

Methylphenidate, as in **PHENITAB** may decrease the effectiveness of medicines used to

treat hypertension.

Use with medicines that elevate blood pressure

Caution is advised in patients being treated with **PHENITAB** with any other medicine that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4). Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive medicines, including **PHENITAB**. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with serotonergic medicines

There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic medicines. If concomitant use of **PHENITAB** with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important (see section 4.4). **PHENITAB** must be discontinued as soon as possible if serotonin syndrome is suspected.

Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned **PHENITAB** treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using **PHENITAB** in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with urinary alkalisers:

The urinary excretion of methylphenidate is reduced by urinary alkalisers, which may enhance or prolong their effects, excretion is increased by urinary acidifiers.

Use with dopaminergic medicines

Caution is recommended when administering **PHENITAB** with dopaminergic medicines, including antipsychotics. Because a predominant action of methylphenidate, as in **PHENITAB**, is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Fertility, pregnancy and lactation

Pregnancy

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have shown evidence of reproductive toxicity at maternally toxic doses.

Teratogenicity has been shown in laboratory animals.

PHENITAB should not be used in pregnancy as safety has not been established (see section 4.3).

Breastfeeding

Methylphenidate, as in **PHENITAB**, is excreted in human milk.

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure, but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the child cannot be excluded.

PHENITAB should not be used during lactation (see section 4.3)

Fertility

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

PHENITAB can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery. This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent	Nasopharyngitis, upper respiratory tract infection, sinusitis
Blood and lymphatic system disorders	Less frequent Frequency unknown	Anaemia, leucopoenia Pancytopenia*, thrombocytopenia*, thrombocytopenia purpura*
Immune system disorders	Less frequent Frequency unknown	Angioedema Hypersensitivity reactions such as angioedema, anaphylactic

		reactions*, auricular swelling*, bullous conditions*, exfoliative conditions*, urticaria*, pruritus NEC*, rashes*, eruptions*, and exanthemas NEC*
Metabolism and nutrition disorders	Frequent	Anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children
Psychiatric disorders	Frequent	Insomnia, nervousness, affect lability, anxiety, depression, irritability, abnormal behaviour, mood swings, tics, initial insomnia, depressed mood, libido decreased, tension, bruxism, panic attack, aggression, agitation
	Less frequent	Psychotic disorders, anger, suicidal ideation, mood altered, restlessness, tearfulness, worsening of pre-existing tics of Tourette's Syndrome, hypervigilance, sleep disorder, libido disorder, confusional state, suicidal attempt (including completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive

	Frequency unknown	behaviours, over-focussing Delusions, thought disturbances, cases of abuse and dependence have been described more often with immediate release formulations, disorientation*, hallucination*, auditory hallucination*, visual hallucination*, mania*, logorrhoea*
Nervous system disorders	Frequent	Headache, dizziness, psychomotor hyperactivity, somnolence, paraesthesia, tension headache
	Less frequent	Sedation, tremor, lethargy, choreo-athetoid movements, reversible ischaemic neurological deficit, Neuroleptic Malignant Syndrome (NMS; reports were poorly documented, and in most cases, patients were also receiving other medicines, so the role of methylphenidate is unclear)
	Frequency unknown	Cerebrovascular disorders (including vasculitis, cerebral haemorrhage, cerebrovascular accidents, cerebral occlusion),

		migraine, dysphemia, convulsion*, grand mal convulsion*, dyskinesia*
Eye disorder	Frequent Less frequent Frequency unknown	Accommodation disorder Blurred vision, dry eye, difficulties in vision accommodation Diplopia*, mydriasis*, visual impairment*
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Frequent Less frequent Frequency unknown	Dysrhythmia, tachycardia, palpitations Chest pain, cardiac arrest, myocardial infarction Angina pectoris, bradycardia, extrasystoles, supraventricular tachycardia, ventricular extrasystoles
Vascular disorders	Frequent Less frequent Frequency unknown	Hypertension Hot flush, cerebral arteritis and/or occlusion, peripheral coldness Raynaud’s phenomenon*
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, oropharyngeal pain Dyspnoea

Gastrointestinal disorders	Frequent Less frequent	Abdominal pain upper, diarrhoea, nausea, abdominal discomfort, vomiting, dry mouth, dyspepsia Constipation
Hepato-biliary disorders	Less frequent Frequency unknown	Hepatic enzyme elevations, abnormal liver function, including acute hepatic failure and hepatic coma Hepatocellular injury
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Pruritis, rash, urticaria Bullous condition, exfoliative conditions, hyperhidrosis, macular rash, erythema multiforme, exfoliative dermatitis, fixed medicine eruption Alopecia*, erythema*
Musculoskeletal, and connective tissue disorders	Frequent Less frequent Frequency unknown	Muscle tightness, muscle spasms Muscle cramps Arthralgia*, myalgia*, muscle twitching*, trismus*
Renal and urinary disorders	Less frequent Frequency unknown	Haematuria, pollakiuria Incontinence
Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Erectile dysfunction Gynaecomastia Priapism, erection increased
General disorders and administration	Frequent	Pyrexia, growth retardation during prolonged use in children, fatigue,

site conditions	Less frequent Frequency unknown	feeling jittery, asthenia, thirst Sudden cardiac death Decreased therapeutic response*, chest pain*, chest discomfort*, decreased drug effect*, hyperpyrexia*
Investigations	Frequent Less frequent Frequency unknown	Changes in blood pressure and heart rate (usually an increase), weight decreased, alanine aminotransferase increased Cardiac murmur Increased blood alkaline phosphatase*, increased blood bilirubin*, increased hepatic enzyme*, decreased platelet count*, abnormal white blood cell count*

* Post-marketing data

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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

Signs and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching,

convulsions, coma, grand mal convulsion, euphoria, confused state, confusion, hallucinations (auditory and/or visual), hyperhidrosis, flushing, headache, hyperpyrexia, tachycardia, palpitations, heart rate increased, sinus dysrhythmias, hypertension, mydriasis, dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage.
Treatment consists of appropriate supportive measures. The patients must be protected against self-injury and against external stimuli that would aggravate overstimulation already present.
Activated charcoal and a cathartic may be administered to detoxify the gut. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for **PHENITAB** over dosage has not been established.

The extended release of methylphenidate from **PHENITAB** should be considered when treating patients with overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

A 1.2 Psychoanaleptics (antidepressants).
Pharmacotherapeutic group: centrally acting sympathomimetics: ATC code: N06BA04

Mechanism of action:

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in attention deficit hyperactivity disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra

neuronal space.

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

5.2 Pharmacokinetic Properties

Absorption:

Following oral administration of extended release methylphenidate to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. The mean pharmacokinetic parameters in 36 adults following the administration of extended release methylphenidate 18 mg once daily are summarised in Table 1.

Table 1. **Mean ± SD Pharmacokinetic Parameters**	
PARAMETERS	Extended release methylphenidate (18 mg once daily) (n = 36)
C_{max} (ng/mL)	3,7 ± 1,0
T_{max} (h)	6,8 ± 1,8
AUC_{inf} (ng-h/mL)	41,8 ± 13,9
$T_{1/2}$ (h)	3,5 ± 0,4

No differences in the pharmacokinetics of extended release methylphenidate were noted following single and repeated once daily dosing indicating no significant accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of extended release methylphenidate.

Dose proportionality: Following administration of extended release methylphenidate in single doses of 18, 36 and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-

methylphenidate Were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose. Following administration of extended release methylphenidate, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once daily extended release methylphenidate doses from 54 to 144 mg/day resulted in linear and dose proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, (alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that there was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple dose study in adolescents ADHD patients aged 13 – 16 administered a dose of (18 to 72 mg/day) of extended release methylphenidate, mean C_{max} and AUC_{TAU} of methylphenidate increased proportionally with respect to the dose.

Distribution:

Plasma methylphenidate concentrations in adults decline bi-exponentially following oral administration. The half-life of both d- and l-isomers of methylphenidate in adults following oral administration of extended release methylphenidate was approximately 3,5 h.

Metabolism and excretion:

In humans, methylphenidate is metabolised primarily by de-esterification to (alpha)-phenyl-piperidine acetic acid (PPAA) which has little or no pharmacologic activity.

After oral dosing of radio labelled methylphenidate in humans, about 90 % of the

radioactivity was recovered in urine. The main urinary metabolite was (PPAA), accounting for approximately 80 % of the dose.

Food effects:

There were no differences in either the pharmacokinetics or the pharmacodynamics performance of extended release methylphenidate when administered after a high fat breakfast in patients. There is no evidence of dose dumping in the presence or absence of food.

Special populations:

Gender:

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for extended release methylphenidate were 36,7 ng.h/mL in men and 37,1 ng.h/mL in women, with no difference noted between the two groups.

Age:

The pharmacokinetics of extended release methylphenidate has not been studied in children less than 6 years of age.

Renal insufficiency:

There is no experience with the use of extended release methylphenidate in patients with renal insufficiency. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of extended release methylphenidate.

Hepatic insufficiency:

There is no experience with the use of extended release methylphenidate in patients with hepatic insufficiency.

PROFESSIONAL INFORMATION FOR PHENITAB

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Hypromellose

Iron oxide black

Macrogol

Magnesium Stearate

Sodium Chloride

Succinic Acid

Tablet coating:

Cellulose Acetate

Macrogol

Opadry Clear (consisting of hypromellose and macrogol)

Colour coating:

PHENITAB 18: Opadry II Yellow (consisting of lactose monohydrate, hypromellose, titanium dioxide, triacetin, yellow iron oxide and red iron oxide)

PHENITAB 27: Opadry II Grey (consisting of lactose monohydrate, hypromellose, titanium dioxide, triacetin, black iron oxide and red iron oxide)

PHENITAB 36: Opadry II White (consisting of lactose monohydrate, hypromellose, titanium dioxide, triacetin)

PHENITAB 54: Opadry II Pink (consisting of lactose monohydrate, hypromellose, titanium dioxide, triacetin and red iron oxide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle tightly closed to protect from moisture.

Use within 30 days of opening the container.

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with white HDPE child resistant cap, and containing two white polyethylene capsules with desiccant.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBERS

PHENITAB 18: 56/1.2/0587

PHENITAB 27: 56/1.2/0588

PHENITAB 36: 56/1.2/0589

PHENITAB 54: 56/1.2/0590

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION