PROFESSIONAL INFORMATION

RADD Range

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

RADD 18 mg (prolonged-release tablet)

RADD 27 mg (prolonged-release tablet)

RADD 36 mg (prolonged-release tablet)

RADD 54 mg (prolonged-release tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RADD 18 mg: Each prolonged-release tablet contains 18 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate 193,50 mg).

RADD 27 mg: Each prolonged-release tablet contains 27 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate 194,25 mg).

RADD 36 mg: Each prolonged-release tablet contains 36 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate 187,50 mg).

RADD 54 mg: Each prolonged-release tablet contains 54 mg methylphenidate hydrochloride.

Contains sugar (lactose monohydrate 174,00 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

RADD 18 mg: Yellow, capsule-shaped, biconvex film-coated tablet with 2392 printed in black ink on one side.

RADD 27 mg: Grey, capsule-shaped, biconvex film-coated tablet with 2393 printed in black ink on one side.

RADD 36 mg: White, capsule-shaped, biconvex film-coated tablet with 2394 printed in black ink on one side.

RADD 54 mg: Red-brown, capsule-shaped, biconvex film-coated tablet with 2395 printed in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

PROFESSIONAL INFORMATION

RADD Range

Patients new to methylphenidate

The recommended starting dose of **RADD** for 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 mg or 36 mg once daily for adults.

Patients currently using methylphenidate

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

Previous methylphenidate daily dose	**Recommended RADD dose**
5 mg methylphenidate hydrochloride twice or three times daily	18 mg once daily
10 mg methylphenidate hydrochloride twice or three times daily	36 mg once daily
15 mg methylphenidate hydrochloride twice or three times daily	54 mg once daily
20 mg methylphenidate hydrochloride twice or three times daily	72 mg once daily

Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate (as contained in **RADD**) 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 between 6 – 12 years. Daily dosage above 72 mg is not recommended in adolescents aged 13 – 18 years. Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended treatment

The long-term use of **RADD** has not been systematically evaluated. The medical practitioner who elects to use **RADD** for extended periods (over 12 months) in patients with ADHD should periodically re-evaluate the long-term usefulness of **RADD** for the individual patient with trials off-treatment to assess the patient's functioning without pharmacotherapy.

Dose reduction and discontinuation

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

Special populations

Elderly:

Use of **RADD** in patients over 65 years has not been established.

Paediatric population:

RADD should not be used in children under the age of 6 years

Method of administration

RADD is administered orally, once daily. As the effects have been shown to be present 12 hours after dosing, **RADD** should be taken in the morning.

RADD must be swallowed whole with adequate liquid and must not be chewed, divided or crushed.

RADD may be administered with or without food.

4.3 Contraindications

RADD is contraindicated in:

- known hypersensitivity to methylphenidate or to any of the excipients in **RADD** (see Section 6.1).
- patients with marked anxiety, tension and agitation, since **RADD** may aggravate these symptoms (see section 4.4)
- patients with glaucoma
- patients diagnosed with phaeochromocytoma
- patients undergoing treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing MAOIs, due to the risk of hypertensive crisis (see section 4.5).

- patients with a family history or diagnosis of Tourette's syndrome (see section 4.4)
- patients diagnosed or with a history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- patients with hyperthyroidism
- 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) (see section 4.4)
- pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke (see section 4.4)
- patients with a history of substance or alcohol abuse
- pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

General

Methylphenidate treatment is not indicated in all children with ADHD, the decision to use **RADD** 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.

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

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

Methylphenidate should not be used in the elderly (over 65) as safety and efficacy have not been established.

Use in children under 6 years of age

RADD should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

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

Controlled studies regarding the safety and efficacy of long-term use of methylphenidate have not been undertaken. **RADD** treatment should not and need not, be indefinite, with treatment generally being discontinued during or after puberty.

Careful monitoring for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders is essential in this patient group.

Psychiatric disorders to be monitored 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.

In the event that extended use (more than 12 months) is required in children and adolescents with ADHD, periodic re-evaluation of the benefits should be undertaken by stopping therapy and assessing the patient's functioning without pharmacotherapy.

It is recommended that **RADD** 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 medicinal product is either temporarily or permanently discontinued.

Cardiovascular status

Patients considered for treatment 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. Should cardiac disease be suspected, further specialist cardiac evaluation is to be undertaken. The development of

symptoms suggestive of cardiac disease (e.g. palpitations, exertional chest pain, unexplained syncope, dyspnoea) during **RADD** treatment require immediate specialist cardiac evaluation.

RADD is contraindicated in patients with hypertension.

ADHD patients whose underlying medical conditions might be compromised by increases in heart rate and/or blood pressure, e.g. heart failure and hypertension, should be closely monitored as methylphenidate increases heart-rate, systolic and diastolic blood pressure. Whilst taking **RADD**, patient blood pressure should be monitored at appropriate intervals in all patients, especially in those with hypertension (see section 4.3). Patients who develop symptoms suggestive of cardiac disease during **RADD** treatment should undergo prompt cardiac evaluation.

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

Cases of sudden death have been reported in ADHD patients, with structural cardiac abnormalities and other serious cardiac disorders, treated with methylphenidate used at usual doses. Although some serious heart problems alone may carry an increased risk of sudden death, **RADD** is not recommended in patients with 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 **RADD** (see section 4.3). Before initiating **RADD** treatment, patients should be assessed for pre-existing

cardiovascular disorders such as congenital long QT syndrome, or a family history of sudden death and ventricular dysrhythmia.

Misuse and cardiovascular events

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

Cerebrovascular disorders

Patients with pre-existing central nervous system (CNS) abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with **RADD**. Patients with additional risk factors (such as a history of cardiovascular disease and/or concomitant medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with **RADD**.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure (as contained in **RADD**). 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 **RADD** and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during **RADD** therapy. These symptoms could include severe headache,

numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

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

Tics

RADD is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history and clinical evaluation for tics or Tourette's syndrome should therefore be established prior to **RADD** treatment.

Regular monitoring for the emergence or worsening of tics during treatment with **RADD** is required.

Growth retardation

Long-term treatment with **RADD** may retard normal growth and weight in children. Careful monitoring is required, patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Depression/Fatigue

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

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing **RADD**. Prior to initiating treatment with **RADD**, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders. Treatment of ADHD with **RADD** should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, **RADD** should not be prescribed (see section 4.3).

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.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in patients without prior history of psychotic illness or mania can be caused by **RADD** at normal doses. In the event manic or psychotic symptoms occur, consideration should be given to a possible causal role for **RADD**, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour

Patients beginning treatment with **RADD** should be monitored for the appearance or worsening of aggressive behaviour or hostility. Aggression is frequently associated with ADHD, however, emergence or worsening of aggression has been reported during treatment with **RADD**. Patients should be monitored at treatment initiation, at every dose adjustment and then at least every 6 months or every visit.

Medical practitioners should evaluate the need for adjustment of the treatment regimen in patients experiencing behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

RADD should be given with caution in the following conditions:

Exacerbation of pre-existing psychotic or manic symptoms

Administration of **RADD** may exacerbate symptoms of behaviour disturbances and thought disorder in psychotic patients.

Abuse, misuse and dependence

RADD should be given cautiously to patients with a history of narcotic dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as comorbid

oppositional-defiant or conduct disorder and bipolar disorder), and previous or current substance abuse should 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, **RADD** may not be suitable.

Seizures

RADD should be used with caution in patients with epilepsy.

Evidence indicates lowering of the convulsive threshold in patients with prior history of seizures, prior EEG abnormalities in absence of seizures, and in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, treatment should be discontinued.

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 **RADD** treatment. Treatment of an underlying psychiatric condition may be necessary, and consideration should be given to a possible discontinuation of **RADD**.

Anxiety, agitation or tension

Worsening of pre-existing anxiety, agitation or tension is associated with **RADD** treatment. Clinical evaluation for anxiety, agitation or tension prior to **RADD** treatment should be undertaken with regular monitoring. **RADD** is contraindicated in patients suffering from these conditions (see section 4.3).

Forms of bipolar disorder

Particular care should be taken in the treatment of ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) due to the risk of possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with **RADD**, 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 section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Visual adverse reactions

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

Haematological effects

The long-term safety of treatment with methylphenidate, as in **RADD** is not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. 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

RADD must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided or crushed. **RADD** is contained within a non-absorbable shell designed to release the medicine at a prolonged rate. The tablet shell together with insoluble core components are eliminated from the body. Patients should not be concerned if they occasionally notice something that resembles a tablet in their stools.

As **RADD** is non-deformable and does not appreciably change shape in the GI tract, **RADD** 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 prolonged release design of the tablet, **RADD** should only be administered to patients who are able to swallow the tablet whole.

Use with serotonergic medicinal products

Serotonin syndrome has been reported following coadministration of methylphenidate with

serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of **RADD** and serotonergic medicines is not recommended as this may lead to the development of serotonin syndrome. If concomitant use of **RADD** 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, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular abnormalities (e.g. tremor, myoclonus, hyperreflexia, incoordination, rigidity), seizures and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). **RADD** must be discontinued as soon as possible if serotonin syndrome is suspected and appropriate treatment instituted.

Withdrawal

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

Drug screening

Methylphenidate 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 **RADD** in patients with renal or hepatic insufficiency.

Priapism

Prolonged and painful erections have been reported in association with methylphenidate, 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.

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

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

Pharmacokinetic interactions

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, studies indicate that methylphenidate (as contained in **RADD**) may inhibit the metabolism of warfarin, anticonvulsants (e.g. phenobarbitone, phenytoin, primidone), and some antidepressants (tricyclic and selective serotonin reuptake inhibitors). It may be necessary to adjust the dosage of these medicines that are already being taken and monitor plasma medicines concentrations (or, in the case of warfarin, coagulation times), when initiating or discontinuing concomitant use of **RADD**.

RADD coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

The stimulant effects of **RADD** are inhibited by chlorpromazine, haloperidol and lithium.

Disulfiram may inhibit the metabolism and excretion of **RADD.**

Pharmacodynamic interactions

Use with centrally acting alpha-2 agonists (e.g. clonidine or dexmedetomidine)

Although no causality for the combination has been established, reports of serious adverse effects, including sudden death, in concomitant use with clonidine or dexmedetomidine have been recorded.

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of **RADD**. It is therefore desirable for patients to abstain from alcohol during treatment (see section 4.4).

Anti-hypertensive medicines

Methylphenidate may decrease the effectiveness of medicines used to treat hypertension.

Use with medicines that elevate blood pressure

Caution is advised in concomitant use with any other medicine that can also elevate blood pressure (see section 4.4).

Due to possible hypertensive crisis, **RADD** is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3).

Urinary alkalinisers

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

Use with anaesthetics

There is a risk of sudden blood pressure and heart rate increase during surgery. If surgery is planned, **RADD** treatment should not be used on the day of surgery.

Use with dopaminergic medicines

Caution is recommended when administering **RADD** with dopaminergic medicines, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, **RADD** 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.

Use with serotonergic medicines

The concomitant use of **RADD** and serotonergic medicines is not recommended as this may lead to the development of serotonin syndrome (see section 4.4).

Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Medicine/Laboratory test

RADD may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Teratogenicity has been shown in laboratory animals.

Breastfeeding

Methylphenidate is excreted in human milk, **RADD** should not be used during breastfeeding (see section 4.3).

Fertility

No relevant effects observed in non-clinical studies.

4.7 Effects on ability to drive and use machines

RADD may cause changes to vision (including blurring, altered visual depth perception), sedation and dizziness, patients should be advised to avoid driving or operating heavy machinery until they know how **RADD** affects them.

4.8 Undesirable effects

Tabulated list of adverse 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 leukopenia, thrombocytopenia, thrombocytopenic purpura Pancytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions, angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus NEC, rashes, eruptions, 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, anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour, mood swings, tics, depressed mood, libido decreased, tension, bruxism, panic attack
	Less frequent	Psychotic disorders, auditory, visual and tactile hallucination, anger, suicidal ideation, mood altered, restlessness, tearfulness, worsening of pre-existing tics of Tourette's syndrome, logorrhoea, hypervigilance, sleep disorder, mania, disorientation, libido disorder, confusional state, suicidal attempt (including completed suicide, transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focussing
Psychiatric disorders… continued	Frequency unknown	Delusions, thought disturbances, dependence, cases of abuse and dependence

Nervous system disorders	Frequent	Headache, dizziness, psychomotor hyperactivity, somnolence, paraesthesia, tension headache
	Less frequent	Sedation, tremor, lethargy, convulsion, choreoathetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome
	Frequency unknown	Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion, migraine, dyskinesia
Eye disorders	Frequent	Accommodation disorder
	Less frequent	Blurred vision, dry eye, difficulties in visual accommodation, visual impairment, diplopia
	Frequency unknown	Mydriasis
Ear and labyrinth disorders	Frequent	Vertigo

Cardiac disorders	Frequent Less frequent Frequency unknown	Disrhythmia, tachycardia, palpitations Chest pain, angina pectoris, cardiac arrest, cardiac dysrhythmias myocardial infarction Supraventricular tachycardia, bradycardia, ventricular extrasystoles, 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, nasal congestion Dyspnoea, nasopharyngitis
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain upper, diarrhoea, nausea, abdominal discomfort, vomiting, dry mouth, dyspepsia Constipation
Hepato-biliary disorders	Less frequent	Hepatic enzyme elevations, abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders	Frequent Less frequent	Alopecia, pruritus, rash, urticaria Angioedema, bullous conditions, exfoliative conditions, hyperhidrosis, macular rash; erythema, erythema multiforme, exfoliative dermatitis, fixed drug eruption
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Arthralgia, muscle tightness, muscle spasms Myalgia, muscle twitching, muscle cramps
Renal and urinary disorders	Less frequent	Haematuria, pollakiuria
Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Erectile dysfunction Gynaecomastia Priapism, erection increased and prolonged erection
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Pyrexia, growth retardation during prolonged use in children, fatigue, irritability, feeling jittery, asthenia, thirst Chest pain, sudden cardiac death, decreased medicine effect Chest discomfort, hyperpyrexia

Investigations	Frequent	Changes in blood pressure and heart rate (usually an increase), decreased weight, increased alanine amino-transferase
	Less frequent	Increased hepatic enzyme, increased blood alkaline phosphatase, increased blood bilirubin, decreased platelet count, abnormal white blood cell-count, cardiac murmur

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. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

Signs and symptoms of **RADD**, in an overdosage, result principally from overstimulation of the CNS and excessive sympathomimetic stimulations. They include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions, coma, grand mal convulsion, euphoria, confusional state, confusion, hallucinations (auditory and/or visual), hyperhidrosis,

delirium, flushing, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus dysrhythmias, hypertension, mydriasis, and dry mouth

Management of overdose:

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events e.g. hypertensive crisis, cardiac dysrhythmias, convulsions. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. For the most current guidance for treatment of symptoms of overdose, the practitioner should consult a certified Poison Control Centre or current toxicological publication.

If the patient is conscious, administration of activated charcoal and a laxative is recommended. In the presence of severe intoxication, a carefully titrated dose of benzodiazepine should be given.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of **RADD** has not been established.

The prolonged release of methylphenidate from **RADD** should be considered when treating patients with overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting sympathomimetics

ATC code: N06BA04

Pharmacological classification:

A 1.2 Psychoanaleptics (antidepressants).

Mechanism of action:

Methylphenidate HCl is a mild 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 noradrenaline 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:

Methylphenidate is readily absorbed. Following oral administration of methylphenidate prolonged-release to adults, the tablet overcoat dissolves, providing an initial maximum concentration at about 1 to 2 hours. The methylphenidate contained in the two internal tablet layers is gradually released over the next several hours. Peak plasma concentrations are

achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease.

Methylphenidate prolonged-release taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption of methylphenidate prolonged-release once daily is generally comparable to conventional immediate release preparations.

Following the administration of methylphenidate prolonged-release 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were: C_{max} 3,7 ± 1,0 (ng/mL), T_{max} 6,8 ± 1,8 (h), AUC_{inf} 41,8 ± 13,9 (ng.h/mL), and $t_{½}$ 3,5 ± 0,4 (h).

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

Dose proportionality: Following administration of prolonged-release methylphenidate in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionally with respect to dose. Following administration of prolonged

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 prolonged 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 medicine (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 adolescent ADHA patients aged 13 – 16, administered a dose of (18 to 72 mg/day) of prolonged release methylphenidate, mean C_{max} and AUC_{TAU} of methylphenidate increased proportionally with respect to the dose.

Distribution:

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of prolonged-release methylphenidate was approximately 3,5 h.

The rate of protein binding of methylphenidate and of its metabolites is approximately 15 %.

The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Biotransformation:

In humans, methylphenidate is metabolised primarily by de-esterification to (alpha)-phenyl-piperidine acetic acid (PPA, approximately 50-fold the level of the unchanged substance) which has little or no pharmacologic activity. In adults, the metabolism of prolonged-release methylphenidate once daily, as evaluated by metabolism to PPA, is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of prolonged-release methylphenidate is similar.

Elimination:

The elimination half-life of methylphenidate in adults following administration of prolonged-release methylphenidate was approximately 3.5 hours.

After oral dosing of radiolabelled methylphenidate in humans, about 90 % of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80 % of the dose.

Food Effects:

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of prolonged-release methylphenidate when administered after a high fat

breakfast on an empty stomach. There is no evidence of dose dumping in the presence of food.

Pharmacokinetics in special patient groups

Gender:

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

Ethnicity:

In healthy adults receiving prolonged-release methylphenidate, dose-adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age:

The pharmacokinetics of prolonged-release methylphenidate has not been studied in children younger than 6 years of age.

Renal insufficiency:

There is no experience with the use of prolonged-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 prolonged-release methylphenidate.

Hepatic insufficiency:

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

5.3 Preclinical safety data

Carcinogenicity

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development

Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Fumaric acid

Hypromellose

Indigo carmine aluminium lake

Iron oxide black (E172)

Iron oxide red (E172)[1,3]

Iron oxide yellow (E172)[1,2]

Lactose monohydrate

Macrogol 3350

Magnesium stearate

Methacrylic acid-methyl methacrylate copolymer (1:1)

Methacrylic acid-methyl methacrylate copolymer (1:2)

Opacode Black S-1-17823

Partially hydrolysed polyvinyl alcohol

Talc

Titanium dioxide (E171)

Triethyl citrate

[1] Applicable to the 18 mg strength only

[2] Applicable to the 27 mg strength only

[3] Applicable to the 54 mg strength only

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 container tightly closed.

6.5 Nature and contents of container

RADD tablets are packed into white, round HDPE bottles with round, white plastic child-resistant screw cap with three break-points, ring and integrated desiccant. Bottles, containing 30 tablets, are packed into printed outer cartons.

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

No special requirements.

PROFESSIONAL INFORMATION

RADD Range

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

RADD 18 mg: A51/1.2/0289

RADD 27 mg: A51/1.2/0290

RADD 36 mg: A51/1.2/0291

RADD 54 mg: A51/1.2/0292

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

February 2021

10. DATE OF REVISION OF THE TEXT