PROFESSIONAL INFORMATION

SCHEDULING STATUS: S6

1. NAME OF THE MEDICINE

Mefedinel™ 18 (prolonged release tablets)

Mefedinel™ 27 (prolonged release tablets)

Mefedinel™ 36 (prolonged release tablets)

Mefedinel™ 54 (prolonged release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MEFEDINEL 18 (prolonged release tablet) contains 18 mg methylphenidate hydrochloride.

Each MEFEDINEL 27 (prolonged release tablet) contains 27 mg methylphenidate hydrochloride.

Each MEFEDINEL 36 (prolonged release tablet) contains 36 mg methylphenidate hydrochloride.

Each MEFEDINEL 54 (prolonged release tablet) contains 54 mg methylphenidate hydrochloride.

MEFEDINEL 18 contains sugar (6,31 mg lactose monohydrate per tablet).

MEFEDINEL 27 contains sugar (8,17 mg lactose monohydrate per tablet).

MEFEDINEL 36 contains sugar (8,43 mg lactose monohydrate per tablet).

MEFEDINEL 54 contains sugar (6,76 mg lactose monohydrate per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MEFEDINEL 18: prolonged release tablets

Light yellow, round, film-coated tablet with a delivery orifice on one side.

MEFEDINEL 27: prolonged release tablets

Light grey, round, film-coated tablet with a delivery orifice on one side.

MEFEDINEL 36: prolonged release tablets

White, round, film-coated tablet with a delivery orifice on one side.

MEFEDINEL 54: prolonged release tablets

Red, round, film-coated tablet with a delivery orifice on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD):

MEFEDINEL is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 to 17 and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

4.2 Posology and method of administration

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

MEFEDINEL 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.

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

MEFEDINEL may be administered with or without food.

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

Patients New to Methylphenidate:

The recommended starting dose of MEFEDINEL prolonged release tablets 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 or 36 mg daily for adults.

Patients Currently Using Methylphenidate:

The recommended dose of MEFEDINEL prolonged release tablets for patients who are currently taking methylphenidate three times daily at doses of 15 to 60 mg/day is provided in Table 1. Dosing recommendations are based on current dose regimen and clinical judgement.

TABLE 1: Recommended Dose Conversion from Other Methylphenidate Regimens to MEFEDINEL *prolonged release tablets*

Previous methylphenidate daily dose	***Recommended MEFEDINEL prolonged release tablets dose***
5 mg Methylphenidate twice daily or three times daily	18 mg once daily
10 mg Methylphenidate twice daily or three times daily	36 mg once daily
15 mg Methylphenidate twice daily or three times daily	54 mg once daily
20 mg Methylphenidate 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 to 12 years and to a maximum of 72 mg for adolescents aged between 13 to 18 years and 108 mg in adults. In general, dosage adjustments may proceed at approximately weekly intervals.

Daily dosage above 54 mg is not recommended for children aged between 6 to 12 years. Daily dosage above 72 mg is not recommended for adolescents aged between 13 to 18 years.

Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended Treatment:

The long-term use of MEFEDINEL has not been systematically evaluated in controlled clinical trials.

The physician who elects to use MEFEDINEL 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 patients 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, MEFEDINEL should be discontinued.

Elderly:

Safety and efficacy have not been established in patients over 60 years of age.

Paediatric population:

Children under 6 years of age:

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

Hepatic impairment:

MEFEDINEL has not been studied in patients with hepatic impairment. Caution should be exercised in these patients.

Renal impairment:

MEFEDINEL has not been studied in patients with renal impairment. Caution should be exercised in these patients.

Method of administration

General recommendations

MEFEDINEL is for oral administration and can be taken with or without food.

4.3 Contraindications

- Known hypersensitivity to methylphenidate or to any of the excipients in MEFEDINEL (see section 6.1).
- Glaucoma.
- Pheochromocytoma.
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicines, due to risk of hypertensive crisis (see section 4.5).

- Hyperthyroidism.
- 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, channelopathies (disorders caused by the dysfunction of ion channels) and QT prolongation either congenital, familial or caused by medication (see section 4.4).
- Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders.
- Anxiety, tension, agitation, a family history or diagnosis of Tourette's syndrome.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Methylphenidate 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.

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

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials.

Methylphenidate treatment should not and need not be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring 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 methylphenidate 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 medicine to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate 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 temporary or permanently discontinued.

Use in adults with ADHD:

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. Safety and efficacy have not been established in this age group.

Use in children under 6 years of age:

MEFEDINEL should not be used in patients under 6 years old. Sufficient data on the safety of long-term use of MEFEDINEL is not yet available.

Cardiovascular status:

Patients who are being considered for treatment with stimulant medicines 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 methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mm Hg relative to controls. The short and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data.

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which methylphenidate treatment is contraindicated.

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 is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric advice has been obtained (see section 4.3).

Sudden death and pre-existing cardiac structural 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 medicines are not recommended in children or adolescents with known cardiac structural 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.

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 medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

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 methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate

therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory. Treatment with methylphenidate 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 medicines. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate 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 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 at usual doses.

If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour:

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate 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. 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.

Suicidal tendency:

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their medical practitioner. 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 methylphenidate.

Tics:

Methylphenidate is 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 methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension:

Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate 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 methylphenidate to treat ADHD in patients with co-morbid bipolar disorder (including untreated type 1 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 methylphenidate, patients with co-morbid 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' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

Growth:

Moderately reduced weight gain and growth retardation have been reported with long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures:

Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with 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, methylphenidate should be discontinued.

Priapism:

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

Use with serotonergic medicinal products:

Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic medicinal products. If concomitant use of methylphenidate with a serotonergic medicinal product 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). Methylphenidate must be discontinued as soon as possible if serotonin syndrome is suspected.

Abuse, misuse and diversion:

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

Methylphenidate 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 methylphenidate 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 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, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal:

Careful supervision is required during withdrawal, since this 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.

Fatigue:

Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Choice of methylphenidate formulation:

The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening:

This product 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 in patients with renal or hepatic insufficiency.

Haematological effects:

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

Because MEFEDINEL prolonged release tablet is non-deformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable prolonged release formulations.

Due to the prolonged-release design of the tablet, MEFEDINEL prolonged release tablets should only be used in patients who are able to swallow the tablet whole. Patients should be informed that MEFEDINEL must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a non-absorbable shell designed to

release the medicines at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Excipients:

MEFEDINEL contains lactose.

Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take MEFEDINEL.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered medicines.

Therefore, caution is recommended at combining methylphenidate 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, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbitone, phenytoin, primodone), and some antidepressants (tricyclic and selective serotonin reuptake inhibitors). When starting and stopping treatment with methylphenidate, 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 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 methylphenidate with other medicines 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 methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics:

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

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

The long-term safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic medicines:

Caution is recommended when administering methylphenidate with dopaminergic medicines, including antipsychotics.

Because a predominant action of methylphenidate 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.

Use with serotonergic medicines:

There have been reports of serotonin syndrome following co-administration of methylphenidate with serotonergic medicines. If concomitant use of MEFEDINEL with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important. MEFEDINEL must be discontinued as soon as possible if serotonin syndrome is suspected.

Medicine/Laboratory test:

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

MEFEDINEL is contraindicated in pregnancy, as safety has not been demonstrated.

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

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses. (See section 5.3.)

Lactation:

Methylphenidate has been found in breast-milk of women treated with methylphenidate. Mothers on MEFEDINEL should not breastfeed their infants.

Fertility:

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

4.7 Effects on ability to drive and use machines

MEFEDINEL may 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.

4.8 Undesirable effects

The table below shows all adverse reactions observed during clinical trials and post-market spontaneous reports with methylphenidate prolonged-release tablets and those which have been reported with other methylphenidate hydrochloride formulations. If the adverse reactions with methylphenidate prolonged-release tablet and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

System Organ Class	***Adverse reaction***		
	Frequency		
	Frequent	***Less frequent***	***Frequency unknown***

Infections and infestations	Nasopharyngitis, upper respiratory tract infection[#], sinusitis[#]		
Blood and lymphatic system disorders		Anaemia[†], leukopenia[†], thrombocytopenia, thrombocytopenic purpura	Pancytopenia
Immune system disorders		Hypersensitivity reactions such as angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rashes, and eruptions	
Metabolism and nutrition disorders*	Anorexia, decreased appetite[†], moderately reduced weight and height		

	gain during prolonged use in children*		
Psychiatric disorders*	Insomnia, nervousness, affect lability, aggression*, agitation*, anxiety*†, depression*#, irritability, abnormal behaviour, mood swings, tics*, initial insomnia#, depressed mood#, libido decreased#, tension#, bruxism#, panic attack#	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*,	Delusions*†, thought disturbances*, dependence; cases of abuse and dependence have been described more often with immediate release formulations

		abnormal thinking, apathy†, repetitive behaviours, over-focusing	
Nervous system disorders	Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, paraesthesia#, tension headache#	Sedation, tremor†, lethargy#, convulsion, choreoathetoid 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).	Cerebrovascular disorders*† (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion*, migraine†, dysphemia

Eye disorders	Accommodation disorder[#]	Blurred vision[†], dry eye[#], difficulties in visual accommodation, visual impairment, diplopia	Mydriasis
Ear and labyrinth disorders	Vertigo[#]		
Cardiac disorders	Dysrhythmia, tachycardia, palpitations	Chest pain, angina pectoris, cardiac arrest; myocardial infarction	Supraventricular tachycardia, bradycardia, ventricular extrasystoles[†], extrasystoles[†]
Vascular disorders	Hypertension	Hot flush[#], cerebral arteritis and/or occlusion, peripheral coldness[†], Raynaud's phenomenon	
Respiratory, Thoracic and mediastinal disorders	Cough, oropharyngeal pain	Dyspnoea[†]	

Gastrointestinal disorders	Upper abdominal pain, diarrhoea, nausea†, abdominal discomfort, vomiting, dry mouth†, dyspepsia#	Constipation†	
Hepatobiliary disorders	Alanine aminotransferase increased#	Hepatic enzyme increased, abnormal liver function, including acute hepatic failure and hepatic coma, blood alkaline phosphatase increased, blood bilirubin increased†	
Skin and subcutaneous tissue disorders	Alopecia, pruritus, rash, urticaria	Angioedema, bullous conditions, exfoliative conditions, hyperhidrosis†, macular rash,	

		erythema, erythema multiforme, exfoliative dermatitis, fixed drug eruption	
Musculoskeletal and connective tissue disorders	Arthralgia, muscle tightness#, muscle spasms#	Myalgia†, muscle twitching, muscle cramps,	Trismus^
Renal and urinary disorders		Haematuria, Pollakiuria	Incontinence
Reproductive system and breast disorders	Erectile dysfunction#	Gynaecomastia	Priapism*, erection increased* and prolonged erection*
General disorders and administration site conditions	Pyrexia, growth retardation during prolonged use in children*, fatigue†, irritability#, feeling jittery#, asthenia#, thirst#	Chest pain, sudden cardiac death*	Chest discomfort†, hyperpyrexia

Investigations	Changes in blood pressure and heart rate (usually an increase)*, weight decreased*	Cardiac murmur*, platelet count decreased, abnormal white blood cell count	

* See section 4.4

Frequency derived from adult clinical trials and not on data from trials in children and adolescents; may also be relevant for children and adolescents.

† Frequency derived from clinical trials in children and adolescents and reported at a higher frequency in clinical trials in adult patients.

^ Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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.

Suspected adverse reactions may also be reported directed to the Holder of Certificate of Registration (HCR) via the link: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from formulations with extended durations of action.

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 (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac dysrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment:

There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures and symptomatic treatment of life-threatening events e.g. hypertensive crisis, cardiac dysrhythmias, convulsions. For the most current guidance for treatment of symptoms of overdose, the medical practitioner should consult a certified Poison Control Centre or current toxicological publication.

The patient must be protected against self-injury and against external stimuli that would aggravate over-stimulation already present. 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 a benzodiazepine should be given.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting sympathomimetics: ATC code: N06BA04.

Mechanism of action

Methylphenidate 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 neurone and increase the release of these monoamines into the extraneuronal 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 tablet to adults the drug overcoat dissolves, providing an initial maximum medicine concentration at about 1 to 2 hours. The methylphenidate contained in the internal drug layer 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 tablet 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 tablet once daily is generally comparable to conventional immediate release preparations.

Following the administration of methylphenidate prolonged release tablet 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 $t_{1/2}$ 3,5 ± 0,4 (h).

No differences in the pharmacokinetics of methylphenidate prolonged release tablet were noted following single and repeated once daily dosing, indicating no significant medicine accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of methylphenidate prolonged-release tablet 18 mg.
Following administration of MEFEDINEL in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC_{inf} of methylphenidate were proportional to dose.

Distribution:

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of methylphenidate prolonged release tablet was approximately 3,5 hours. The rate of protein binding of methylphenidate and of its metabolites is approximately 15 %. The apparent volume of distribution of methylphenidate is approximately 13 L/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 methylphenidate prolonged-release tablet 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 methylphenidate prolonged-release tablet is similar.

Elimination:

After oral administration, about 90 % of the dose is excreted in urine and 1 to 3 % in faeces, as metabolites within 48 to 96 hours. Small quantities of unchanged methylphenidate are recovered in urine (less than 1 %). The main urinary metabolite is alpha-phenyl-piperidine acetic acid (60 to 90 %).

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.

The elimination half-life of methylphenidate in adults following administration of methylphenidate prolonged release tablet was approximately 3,5 hours.

Food Effects:

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of MEFEDINEL when administered after a high fat breakfast on an empty stomach.

Special Populations:

Gender:

In healthy adults, the mean dose-adjusted AUC_{inf} values for MEFEDINEL were 36,7 ng.h/mL in men and 37,1 ng.h/mL in women, with no differences noted between the two groups.

Race:

In healthy adults receiving MEFEDINEL, dose-adjusted AUC_{inf} was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age:

The pharmacokinetics of MEFEDINEL has not been studied in children younger than 6 years of age. In children 7 to 12 years of age, the pharmacokinetics of MEFEDINEL after 18, 36 and 54 mg were (mean ± SD): C_{max} 6,0 ± 1,3, 11,3 ± 2,6, and 15,0 ± 3,8 ng/mL, respectively, T_{max} 9,4 ± 0,02, 8,1 ± 1,1, 9,1 ± 2,5 h, respectively, and $AUC_{0-11,5}$ 50,4 ± 7,8, 87,7 ± 18,2, 121,5 ± 37,3 ng.h/mL, respectively.

Renal Insufficiency:

There is no experience with the use of MEFEDINEL in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80 % of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of MEFEDINEL.

Hepatic Insufficiency:

There is no experience with the use of MEFEDINEL in patients with hepatic insufficiency.

5.3 Preclinical safety data

Carcinogenicity:

In lifetime 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

Medicine layer:

Butylhydroxytoluene, polyethylene oxide, povidone (K 25), stearic acid and succinic acid.

Push layer:

Butylhydroxytoluene, iron oxide red (E 172), polyethylene oxide, povidone (K 25), sodium chloride and stearic acid.

Membrane layer:

Cellulose acetate and poloxamer 188.

Medicine coat:

Hypromellose and succinic acid.

Film coat:

Lactose monohydrate, hypromellose, macrogol 4000 and titanium dioxide (E171).

In addition:

MEFEDINEL 18, 54: Iron oxide yellow (E 172) and Iron oxide red (E 172).

MEFEDINEL 27: Iron oxide black (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

MEFEDINEL 18, 27, 36, 54: HDPE bottles closed with a child-resistant, tamper evident PP screw cap with drying plug.

Pack sizes of 28, 30, 50, 56, 60, 98, 100 or 120 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

MEFEDINEL 18: 48/1.2/0092

MEFEDINEL 27: 48/1.2/0093

MEFEDINEL 36: 48/1.2/0094

MEFEDINEL 54: 48/1.2/0095

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 February 2021

10. DATE OF REVISION OF THE TEXT

19 October 2022

[1]Company Reg. No.: 1990/001979/07