Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	MEFEDINEL 10
Dosage form and strength	:	Tablet. Each tablet contains 10 mg methylphenidate hydrochloride.

PROFESSIONAL INFORMATION FOR MEFEDINEL 10

SCHEDULING STATUS: S6

1 NAME OF THE MEDICINE

MEFEDINEL 10 (tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MEFEDINEL 10 (tablet) contains 10 mg methylphenidate hydrochloride.

MEFEDINEL 10 contains sugar (42,99 mg lactose monohydrate per tablet)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White, round, bevelled flat tablet, scored on both sides and radially.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications:

MEFEDINEL 10 is indicated for treatment of attention-deficit hyperactivity disorder (ADHD) in children aged 6 years and older.

MEFEDINEL 10 is indicated for treatment of narcolepsy in adults.

4.2. Posology and method of administration

Posology:

The dosage of MEFEDINEL 10 should be individualised according to the patient's clinical needs and responses.

MEFEDINEL 10 should be started at a low dose, with increments at weekly intervals.

Daily doses above 60 mg are not recommended for the treatment of narcolepsy in adults, or for the treatment of ADHD in children. Effective doses in adults may vary and range from 40 - 80 mg per day.

If improvement is not observed after appropriate dosage adjustment over a one-month period, MEFEDINEL 10 should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, MEFEDINEL 10 should be discontinued.

Pre-treatment screening:

Before initiating MEFEDINEL 10 treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular dysrhythmia and psychiatric disorders (see sections 4.3 and 4.4).

Narcolepsy:

The average dosage is 20 to 30 mg daily given in 2 to 3 divided doses. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate.

Patients who are unable to sleep if medicine is taken late in the day should take the last dose before 6 p.m.

A total daily dose of 60 mg should not be exceeded.

ADHD:

Children and adolescents (6 years and over): Start with 5 mg once or twice daily (e.g. at breakfast and lunch), with gradual increments of 5 -10 mg weekly.

The total daily dose should be administered in divided doses.

Daily dosage above 60 mg daily is not recommended.

Periodic assessment of the treatment in ADHD:

Medicine treatment should not and need not be indefinite.

MEFEDINEL 10 should be periodically discontinued to assess the patient's condition.

Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

When used in children with ADHD, MEFEDINEL 10 can usually be discontinued after puberty.

Special populations:

Elderly

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

Hepatic impairment

MEFEDINEL 10 has not been studied in patients with hepatic impairment.

Renal impairment

MEFEDINEL 10 has not been studied in patients with renal impairment.

Paediatric population

Children under 6 years of age:

MEFEDINEL 10 should not be used in children under the age of 6 years.

Method of administration:

General recommendations

MEFEDINEL 10 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 10 (see sections 6.1).
- Glaucoma.
- Phaechromocytoma.
- During treatment with 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 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 1) 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) 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

MEFEDINEL 10 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, as contained in MEFEDINEL 10 has not been systematically evaluated in controlled trials.

MEFEDINEL 10 treatment should not and need not be indefinite. MEFEDINEL 10 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 nevo* 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 MEFEDINEL 10 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 MEFEDINEL 10 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 with ADHD:

MEFEDINEL 10 is not indicated for use in adults with ADHD. Safety and efficacy have not yet been established in this age group.

Use in the elderly:

MEFEDINEL 10 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 10 should not be used in patients under 6 years old. Sufficient data on the safety of long-term use of MEFEDINEL 10 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 mmHg 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 centile chart at each adjustment of dose and then at least every 6 months.

The use of MEFEDINEL 10 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 MEFEDINEL 10 treatment is contraindicated. 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 methylphenidate**.** 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 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 be given with caution.

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 MEFEDINEL 10 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 MEFEDINEL 10 treatment. Treatment of an underlying psychiatric condition may be necessary, and consideration should be given to a possible discontinuation of methylphenidate.

Tics:

Methylphenidate, as contained in MEFEDINEL 10, 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, as contained in MEFEDINEL 10, 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 MEFEDINEL 10 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 MEFEDINEL 10, 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')**.** Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

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. Priapism has also been reported during a period of medicine withdrawal (drug holidays or during discontinuation).

Growth retardation:

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 MEFEDINEL 10 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:

MEFEDINEL 10 should be used with caution in patients with epilepsy. MEFEDINEL 10 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.

Use with serotonergic medicines:

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). 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, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia, dizziness, diaphoresis, flushing), neuromuscular abnormalities (e.g. tremor, myoclonus, hyperreflexia, incoordination, rigidity), seizures 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 MEFEDINEL 10.

MEFEDINEL 10 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 MEFEDINEL 10 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, as contained in MEFEDINEL 10, or other stimulants may not be suitable and nonstimulant 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:

MEFEDINEL 10 should not be used for the prevention or treatment of normal fatigue states.

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 leucopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Paediatric patients under 6 years of age:

MEFEDINEL 10 is not indicated in children less than six years of age. Treatment with MEFEDINEL 10 is not indicated in all cases of Attention-Deficit/Hyperactivity disorder and should be considered only after detailed history-taking and evaluation. The decision to prescribe MEFEDINEL 10 should depend on the medical practitioner assessment of the chronicity and severity of the child's symptoms and, their appropriateness to the child's age. Prescription should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with methylphenidate is not indicated.

Excipients:

MEFEDINEL 10 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MEFEDINEL 10.

4.5. Interaction with other Medicines and other forms of interaction

Pharmacokinetic interaction:

It is not known how methylphenidate, as contained in MEFEDINEL 10, may affect plasma concentrations of concomitantly administered medicines.

Therefore, caution is recommended at combining methylphenidate with other medicines, especially those with 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, primidone), 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 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* or dexmedetomidine*)

The long-term safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated. Serious adverse events including sudden death may occur in concomitant use with clonidine or dexmedetomidine, although no causality for the combination has been established.

Use with dopaminergic medicines

Caution is recommended when administering methylphenidate with dopaminergic medicines, including antipsychotics. Because a predominant action of methylphenidate is to increase extra cellular 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. The coadministration of MEFEDINEL 10 with antipsychotics is not recommended because of the counteracting mechanism of action.

Use with serotonergic medicines

There have been reports of serotonin syndrome following co-administration of methylphenidate with serotonergic medicines. If concomitant use of MEFEDINEL 10 with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important. MEFEDINEL 10 must be discontinued as soon as possible if serotonin syndrome is suspected. Methylphenidate has been shown to increase extracellular serotonin and norepinephrine and appears to have weak potency in binding serotonin transporter.

Medicine/Laboratory test:

MEFEDINEL 10 may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

4.6 Fertility, pregnancy and lactation

Pregnancy:

MEFEDINEL 10 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.

Breastfeeding:

Methylphenidate has been found in breast milk of a woman treated with methylphenidate.

Mothers on MEFEDINEL 10 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 10 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 drug reactions (ADRs) observed during clinical trials and post market spontaneous reports with methylphenidate and those which have been reported with other methylphenidate hydrochloride formulations. If ADRs with methylphenidate and the other 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.	Gastroenteritis	
Blood and lymphatic system disorders		Anaemia†, Leucopenia†, Thrombocytopenia, Thrombocytopenic purpura	Pancytopenia
Immune system disorders		Hypersensitivity reactions such as Angioneurotic oedema , Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, 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# Sleep disorder Restlessness†	Psychosis (sometimes with visual and tactile hallucinations), Auditory 7 hallucination* Anger, Suicidal ideation*, Mood altered, Tearfulness, Worsening of pre-existing tics of Tourette's syndrome*, Logorrhoea, Hypervigilance, Mania*†, Disorientation, Libido disorder, Confusional state† Suicidal attempt (Including completed suicide) *†, Transient depressed mood*, Abnormal thinking,	Delusions*†, Thought disturbances*, Dependence. Cases of abuse and dependence have been described, more often with immediate release formulations

		Apathy†, Repetitive behaviours, Overfocussing Hyperactivity	
Nervous system disorders	Headache, Dizziness, Drowsiness Dyskinesia, Psychomotor hyperactivity, Somnolence, Paresthaesia#, Tension headache# Tremor†	Sedation, Lethargy# Convulsion, Choreoathetoid movements, Cerebrovascular disorders*† (Including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Reversible ischaemic neurological deficit, Neuroleptic malignant Syndrome (NMS:	

		Reports were Poorly documented and in most cases, patients were also receiving other drugs, so, the role of methylphenidate is unclear). Tics or exacerbation of existing tics and Tourette's syndrome	
Eye disorders		Blurred vision†, Dry eye# Difficulties in visual accommodation, Visual disturbance, Diplopia	Mydriasis
Cardiac disorders	Dysrhythmia, Tachycardia, Palpitations	Chest pain Angina pectoris Cardiac arrest; Myocardial infarction	Supraventricular tachycardia, Bradycardia,

			Ventricular extrasystoles†, Extrasystoles†
Vascular disorders	Hypertension, Peripheral coldness†, Raynaud's phenomenon	Hot flush# Cerebral arteritis and/or occlusion,	
Respiratory, Thoracic and mediastinal disorders	Cough, Oropharyngeal pain Dyspnoea†		Epistaxis
Gastrointestinal Disorders	Abdominal pain upper, Diarrhoea, Nausea†, Abdominal discomfort, Vomiting, Dry mouth†, Dyspepsia# Toothache	Constipation†	
Hepatobiliary disorders		Hepatic enzyme Increased,	

		Abnormal liver function, including hepatic coma**,**	
Skin and subcutaneous tissue disorders	Alopecia, Pruritus, Rash, Urticaria, Fever, Hyperhidrosis*	Angioedema, Bullous conditions, Exfoliative conditions, Macular rash; Erythema Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption, Thrombocytopenic purpura	
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia†, Muscle Twitching, Muscle tension Muscle cramps	Trismus
Renal and urinary disorders			Haematuria Incontinence
Reproductive system and breast disorders		Gynaecomastia	Priapism*, Erection increased and prolonged

			erection*
General disorders and administration site conditions	Pyrexia, Fatigue†, Feeling jittery#, Thirst#	Chest pain, Sudden cardiac death*, Growth retardation during prolonged use in children*	Chest discomfort†, Hyperpyrexia
Investigations	Changes in blood pressure and heart rate (usually an increase)*, Weight decreased*	Cardiac murmur* Platelet count decreased, White blood cell count Abnormal Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal	

* 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 adolescent and reported at a higher frequency in clinical trials in adult patients.

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 providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the HCR via the website: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com

4.9 Overdose

Signs and symptoms:

Vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitation, cardiac dysrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment:

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 practitioner should consult a certified Poison Control Centre or current toxicological publication.

Supportive measures include protection of the patient against self-injury and against external stimuli that would exacerbate the overstimulation already present. If the overdose is oral and the patient is conscious, administration of activated charcoal is recommended.

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 overdosage of MEFEDINEL 10 has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: psychostimulants - ATC code: NO6B AO4.

Methylphenidate is a racemate, consisting of a 1:1 mixture of d-methylphenidate and l-methylphenidate.

Mode of action: Methylphenidate is a central nervous system (CNS) stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood but its effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.

The mechanism by which methylphenidate exerts its mental and behavioural effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system.

Methylphenidate is a racemic mixture containing d- and l-enantiomers, where the d-enantiomer is considered as the pharmacologically active enantiomer.

5.2. Pharmacokinetic properties

Absorption:

The active substance methylphenidate hydrochloride is rapidly and almost completely absorbed from the tablets.

Owing to extensive first-pass metabolism the absolute bioavailability was 22 ± 8 % for the d-enantiomer and 5 ± 3 % for the l-enantiomer. Ingestion together with food increased both the peak plasma concentration (C_{max}) by 23 % and the area under the concentration-time curve (AUC) by 15 % but had no relevant effect on the rate of absorption of methylphenidate. Peak plasma concentrations of approximately 40 nmol/L (11 ng/mL) are attained, on average, 1-2 hours after administration of 0,30 mg/kg. The peak plasma concentrations, however, show considerable intersubject variability. The AUC and the Cmax, are proportional to the dose.

Distribution:

In the blood, methylphenidate and its metabolites become distributed in the plasma (57 %) and the erythrocytes (43 %). Methylphenidate and its metabolites have a low plasma protein-binding rate (10-33 %). The apparent distribution volume has been calculated as 13,1 L/kg after an oral dose; the volume of distribution after intravenous dose (Vss) is 2,23 L/kg for the racemate in healthy adult volunteers.

The volume of distribution was 2,65 ± 1,11 L/kg for dextromethylphenidate (d-MPH) and 1,80 ± 0,91L/kg for levomethylphenidate (l-MPH). Methylphenidate is excreted in breast milk.

Biotransformation:

Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Peak plasma concentrations of α-phenyl-2-piperidyl acetic acid (ritalinic acid) (PPAA) are attained approximately 2 hours after

administration of methylphenidate and are 30-50 times higher than those of the unchanged substance. The half-life of PPAA is roughly twice as long as that of methylphenidate, and the mean systemic clearance is 0.17 L/h/kg.

Elimination:

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours, The systemic clearance is 0,40 ± 0,12 L/h/kg for d-MPH and 0,73 ± 0,28 L/h/kg for l-MPH. Within 48-96 hours 78-97 % of the dose administered is excreted in the urine and 1-3 % in the faeces in the form of metabolites. Unchanged methylphenidate appears in the urine only in small quantities (<1 %). The bulk of the dose is excreted in the urine as PPAA, (60-86 %).

Characteristics in patients:

There are no apparent differences in the pharmacokinetic behaviour of methylphenidate in hyperactive children and healthy adult volunteers.

Elimination data from patients with normal renal function suggest that renal excretion of the unchanged methylphenidate would hardly be diminished at all in the presence of impaired renal function. However, renal excretion of PPAA may be reduced.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium hydrogen phosphate dihydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep blisters in the outer carton until required for use.

Do not use after the expiry date stated on the label / carton.

6.5. Nature and contents of container

Round, white HDPE bottle, white polypropylene cap with permaseal liner, or

White opaque PVC film sealed with aluminium push through foil, or

White opaque PVC/PE/PVdC film sealed with aluminium push through foil. The blister strips are packed in an outer cardboard carton.

Pack size of 30 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	MEFEDINEL 10
Dosage form and strength	:	Tablet. Each tablet contains 10 mg methylphenidate hydrochloride.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

58/1.2/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization

09 June 2026

10. DATE OF REVISION OF THE TEXT

Not applicable

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