Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metidate XL 18 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 18 mg of methylphenidate hydrochloride.
Excipient(s) with known effect: contains 5.99 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Light yellow film-coated tablet of round shape (diameter 8 mm) with a delivery orifice (visible round small hole) on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Attention-Deficit/Hyperactivity Disorder (ADHD)

Metidate XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to the current DSM criteria or ICD guidelines and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptoms.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Metidate XL treatment is not indicated in all children with ADHD and the decision to use the drug 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.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing/diagnostic guidelines.

4.2 Posology and method of administration

Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

Pre-treatment screening

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4).

Ongoing monitoring

Growth, psychiatric and cardiovascular status should be continuously monitored (see also section 4.4).

• Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;

• Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;

• Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

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

Posology

Dose titration

Careful dose titration is necessary at the start of treatment with Metidate XL. Dose titration should be started at the lowest possible dose. For those who wish to prescribe between the 18 mg and 36 mg dosages a 27 mg dosage strength is available from other pharmaceutical companies.Other strengths of this medicinal product and other methylphenidate-containing products may be available.

Dosage may be adjusted in 18 mg increments. In general, dosage adjustment may proceed at approximately weekly intervals.

The maximum daily dosage of Metidate XL is 54 mg.

Patients New to Methylphenidate: Clinical experience with methylphenidate prolonged-release tablets is limited in these patients (see section 5.1). Metidate XL may not be indicated in all children with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be considered sufficient to treat patients new to methylphenidate. Careful dose titration by the physician in charge is required in order to avoid unnecessarily high doses of methylphenidate. The recommended starting dose of Metidate XL for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate: The recommended dose of Metidate XL for patients who are currently taking methylphenidate three times daily at doses of 15 to 45 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 Hydrochloride Regimens, where available, to Metidate XL

Previous Methylphenidate Hydrochloride Daily Dose	**Recommended Metidate XL Dose**
5 mg methylphenidate three times daily	18 mg once daily
10 mg methylphenidate three times daily	36 mg once daily
15 mg methylphenidate three times daily	54 mg once daily

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

Long-term (more than 12 months) use 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. The physician 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 medicinal product for the individual patient with trial periods off medication 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 (preferable during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued

Adults

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with methylphenidate in adults is not appropriate (see sections 4.4 and 5.1).

Elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age

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

Method of administration

Metidate XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see section 4.4).

Metidate XL may be administered with or without food (see section 5.2).

Metidate XL is taken once daily in the morning.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

• Glaucoma

• Phaeochromocytoma

• During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to the 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 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 arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)

• Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug 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 according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician 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 medicinal product for the individual patient with trial periods off medication 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 medicinal product is either temporarily or permanently discontinued.

Use in adults

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

Use in the elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in children under 6 years of age

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

Cardiovascular status
Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) 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. The possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data especially when treatment during childhood/adolescence is continued into adulthood.
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 in 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 cardiac advice has been obtained (see section 4.3).**

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

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

Cerebrovascular disorders
See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with 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 products. 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. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. 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 comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' 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 the 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 rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

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 all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.
For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal
Careful supervision is required during drug 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.

Excipients: galactose intolerance

This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 the methylphenidate 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 drugs in non-deformable prolonged-release formulations.
Due to the prolonged-release design of the tablet, Metidate XL should only be used in patients who are able to swallow the tablet whole. Patients should be informed that Metidate XL 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 drug 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, 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. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive drugs
Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug 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 effect of psychoactive medicinal products, 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 drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of methylphenidate in pregnant women.
Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

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

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Breast-feeding
Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate.

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

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

The table below shows all adverse reactions observed during clinical trials of children, adolescents, and adults and post-market spontaneous reports with methylphenidate prolonged-release tablet 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.

Frequency estimate:
very common (≥1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥1/1000 to < 1/100)
rare (≥1/10,000 to < 1/1000)
very rare (< 1/10,000)
not known (cannot be estimated from the available data).

System Organ Class	**Adverse Reaction Frequency**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations		Nasopharyngitis, Upper respiratory tract infection[#], Sinusitis[#]				
Blood and lymphatic system disorders					Anaemia[†], Leucopenia[†], Thrombocyt -openia, Thrombo-cytopenic 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#	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	Delusions*†, Thought disturbances*, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence, Paresthaesia#, 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 drugs, so the role of methylphenidate is unclear).	Cerebrovascular disorders*† (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion*, Migraine†
Eye disorders		Accommodation disorder#	Blurred vision†, Dry eye#	Difficulties in visual accommodation, Visual		Mydriasis

			impairment, Diplopia		
Ear and labyrinth disorders	Vertigo[#]				
Cardiac disorders*	Arrhythmia, 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	Abdominal pain upper, 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, Pruritis, Rash, Urticaria	Angioneurotic oedema, 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	
Renal and urinary disorders		Haematuria, Pollakiuria			

Reproductive system and breast disorders	Erectile dysfunction#		Gynaeco-mastia		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, White blood cell 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage.
Treatment consists of appropriate supportive measures.
The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. The efficacy of activated charcoal has not been established.
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 methylphenidate has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting sympathomimetics: ATC code: N06BA04

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 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.

Clinical efficacy and safety
In the pivotal clinical studies, methylphenidate prolonged-release tablet was assessed in 321 patients already stabilised with immediate release preparations (IR) of methylphenidate and in 95 patients not previously treated with IR preparations of methylphenidate.
Clinical studies showed that the effects of methylphenidate prolonged-release tablet were maintained until 12 hours after dosing when the product was taken once daily in the morning.

Eight hundred ninety-nine (899) adults with ADHD aged 18 to 65 years were evaluated in three double-blind, placebo-controlled studies of 5 to 13 weeks duration. Some short-term efficacy has been demonstrated for methylphenidate prolonged-release tablet in a dosage range of 18 to 72 mg/day, but this has not been consistently shown beyond 5 weeks. In one study, in which response was defined as at least a 30% reduction from baseline in Conners' Adult ADHD Rating Scales (CAARS) ADHD Symptoms total score at Week 5 (endpoint) and analysed assuming subjects with missing data at their final visit were non-responders, a significantly higher proportion of patients responded to treatment with methylphenidate prolonged-release tablet at doses of 18, 36, or 72 mg/day compared to placebo. In the two other studies, when analysed assuming subjects with missing data at their final visit were non-responders, there were numerical advantages for methylphenidate prolonged-release tablet compared to placebo but a statistically significant difference in the proportion of patients meeting predefined response criteria was not demonstrated between methylphenidate prolonged-release tablet and placebo.

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 drug 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 $t_{½}$ 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 drug 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 methylphenidate prolonged-release tablet in single doses of 18, 36, and 54 mg/day to adults, C_{max} and $AUC_{(0\text{-}inf)}$ 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 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 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

The elimination half-life of methylphenidate in adults following administration of methylphenidate prolonged-release tablet was approximately 3.5 hours. 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 (60-90%).

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.

Food Effects

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

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-inf})}$ values for methylphenidate prolonged-release tablet 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 methylphenidate prolonged-release tablet, 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 methylphenidate prolonged-release tablet has not been studied in children younger than 6 years of age. In children 7-12 years of age, the pharmacokinetics of methylphenidate prolonged-release tablet 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 $AUC_{0\text{-}11.5}$ 50.4±7.8, 87.7±18.2, 121.5±37.3 ng.h/mL, respectively.

Renal impairment

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

Hepatic impairment

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

Drug layer

Polyethylene oxide
Succinic acid
Povidone (K 25)
Butylhydroxytoluene
Stearic acid

Push layer
Polyethylene oxide
Sodium chloride
Povidone (K 25)
Butylhydroxytoluene
Iron oxide red (E 172)
Stearic acid

Membrane layer
Cellulose acetate
Poloxamer 188

Drug coat
Hypromellose
Succinic acid

Film coat
film coating mixture
consisting of:
- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E 171)

- Macrogol 4000
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 2 years.
After first opening of the bottle: 6 months.
After first opening of the bottle: Store below 25°C.

6.4 Special precautions for storage

Unopened bottle: This medicinal product does not require any special storage conditions.
For storage condition after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with a child-resistant polypropylene closure (PP screw cap) with drying plug.

28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/200/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th April 2012

Date of last renewal: 23rd July 2016

10 DATE OF REVISION OF THE TEXT

June 2017