SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methylphenidate Hydrochloride 2mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the oral solution contains 2 mg methylphenidate hydrochloride.
Excipients with known effect:
Propylene glycol 90mg/ml,
Sorbitol 175mg/ml,
Sodium benzoate 1mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methylphenidate is indicated as a 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 DSM criteria or the guidelines in ICD 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 symptom.

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.

Methylphenidate treatment is not indicated in all children with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity and the 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 the way according to the licensed indication and according to the prescribing/diagnostics 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 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.

Dose titration

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

The maximum daily dose is 60mg.

Other strengths of this medicinal product and other methylphenidate containing products may be available.

Children: (over 6 years). Begin with 5mg once or twice daily (e.g. at breakfast and lunch), increasing the dose and frequency of administration if necessary by weekly increments of 5-10mg in the daily dose. Doses above 60mg daily are not recommended. The total daily dose should be administered in divided doses. Methylphenidate is not indicated in children less than 6 years of age.

If the effect of the drug wears off too early in the evening, disturbed behaviour and/or inability to go to sleep may recur. A small evening dose may help to solve this problem.

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 drug 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 school holidays). Improvement may be sustained when the drug 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

Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not yet been established in this age group.

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.

Hepatic impairment

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

Renal impairment

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

Method of administration

The oral solution should be swallowed with a drink of water.

4.3 Contraindications

- Known sensitivity to methylphenidate or to any of the excipients in medicine.
- Glaucoma
- Phaechromocytoma
- During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, 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 arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders

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 section 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 drug 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 drug is either temporary or permanently discontinued.

Use in adults

Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not yet been established in this age group.

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

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 products 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 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 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 least every 6 months and every visit. Physicians 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 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 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.**

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.

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 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.

Increased intraocular pressure and glaucoma

There have been reports of increased intraocular pressure (IOP) and glaucoma (including open angle glaucoma and angle closure glaucoma) associated with methylphenidate treatment (see section 4.8). Patients should be advised to contact their doctor in case of experiencing symptoms suggestive of increased IOP and glaucoma. An ophthalmologist should be consulted and discontinuation of methylphenidate be considered if IOP increases (see section 4.3). Ophthalmologic monitoring of patients with a history of increased IOP is recommended.

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 in to 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 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

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

Excipients with known effects

Sorbitol: This medicine contains 175mg sorbitol in each ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. This medicine may also cause gastrointestinal discomfort and mild laxative effect. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Propylene glycol: This medicine contains 90mg propylene glycol in each ml. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or human, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on case by case basis.

Sodium benzoate: This medicine contains 1mg sodium benzoate in each ml.

Sodium: This medicine contains less than 1mmol sodium (23mg) per ml, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, 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. Phenobarbital, 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 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 other drugs that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4 Warnings and precautions for use).

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with MAO-inhibitors (see section 4.3 Contraindications).

Use with alcohol

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

Use with anaesthetics

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

Use with centrally acting alpha-2agonists (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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

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, Preclinical Safety Data).

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 breast-milk of a women 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

No human data on the effect of methylphenidate on fertility are available. Methylphenidate did not impair fertility in male or female mice (see Section 5.3 Preclinical Safety Data).

4.7 Effects on ability to drive and use machines

Methylphenidate 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 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 available data).

Infections and infestations

Common: Nasopharyngitis

Blood and lymphatic disorders

Very rare: Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura

Not known: Pancytopenia

Immune system disorders

Uncommon: Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritis, rashes and eruptions

Metabolism and nutritional disorders *

Common: Anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children.

Psychiatric disorders *

Very common: Insomnia, nervousness

Common: Anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour, bruxism.

Uncommon: Psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder

Rare: Mania*, disorientation, libido disorder, obsessive-compulsive disorder (including trichotillomania and dermatillomania)

Very rare: Suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy

Not known: Delusions*, thought disturbances*, confusional state, dependence, logorrhea.

Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

Nervous system disorders:

Very common: Headache

Common: Dizziness, dyskinesia, psychomotor hyperactivity, somnolence

Uncommon: Sedation, tremor

Very rare: Convulsions, choreo-athetoid 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).

Not known: Cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine, dysphemia.

Eye disorders

Uncommon: Diplopia, blurred vision, dry eye***

Rare: Difficulties in visual accommodation, mydriasis, visual disturbance

Not known: Increased intraocular pressure, glaucoma

Cardiac disorders*

Common: Arrhythmia, tachycardia palpitations

Uncommon: Chest pain

Rare: Angina pectoris

Very rare: Cardiac arrest, myocardial infarction

Not known: Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*

Common: Hypertension

Very rare: Cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Common: Cough, pharyngolaryngeal pain

Uncommon: Dyspnoea

Not known: Epistaxis

Gastro-intestinal disorders:

Common: Abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting. These usually occur at the beginning of treatment and may be alleviated by concomitant food intake. Dry mouth.

Uncommon: Constipation

Hepatobiliary disorders

Uncommon: Hepatic enzyme elevations

Very rare: Abnormal liver functions, including hepatic coma

Skin and subcutaneous tissue disorders

Common: Alopecia, pruritis, rash, urticaria

Uncommon: Angioneurotic oedema, bullous conditions, exfoliate conditions

Rare: Hyperhidrosis, macular rash, erythema

Very rare: Erythema multiforme, exfoliate dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders

Common: Arthralgia

Uncommon: Myalgia, muscle twitching,

Very rare: Muscle cramps

Not known: Trismus **

Renal and urinary disorders

Uncommon: Haematuria

Not known: Incontinence

Reproductive system and breast disorders

Rare: Gynaecomastia

Not known: Erectile dysfunction, priapism, erection increased and prolonged erection

General disorders and administration site conditions

Common: Pyrexia, growth retardation during prolonged use in children*

Uncommon: Chest pain, fatigue

Very rare: Sudden cardiac death*

Not known: Chest discomfort, hyperpyrexia

Investigations

Common: Changes in blood pressure and heart rate (usually an increase)*, weight decreased*

Uncommon: Cardiac murmur*, hepatic enzyme increased

Very rare: Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

* See section 4.4 “Special warnings and precautions for use”

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, dryness of mucous membranes and rhabdomyolysis.

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 over-stimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given before performing gastric lavage.

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: psychostimulants - ATC code: NO6B AO4.

Mode of action: Methylphenidate is a mild 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 oral solution. 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 (Cmax) 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 40nmol/litres (11ng/ml) are attained, on average, 1-2 hours after administration of 0.30mg/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 volume of distribution was 2.65±1.11 L/kg for d-MPH and 1.80±0.91 L/kg for l-MPH.

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 litres/h/kg. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) are detectable. Therapeutic activity seems to be principally due to the parent compound.

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.

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

Propylene glycol (E 1520)

Glycerol (E 422)

Macrogol 1500

Sodium benzoate (E211)

Liquid Sorbitol (Non – Crystallising) (E420)

Hydrochloric acid (for pH-adjustment)

Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

18 months (unopened)

30 days (once opened)

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

150ml amber glass bottle with plastic child-resistant and tamper evident cap. It contains a 5ml oral syringe with 0.25ml graduations.

Where higher doses are to be administered, dosing cups should be considered.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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