SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Meflynate XL 40 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release capsule contains 40 mg methylphenidate hydrochloride (equivalent to 34.6 mg methylphenidate).

Excipient with known effect

Each capsule contains 238.9 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Hard gelatin capsule size 1, dark yellow opaque, imprinted with “RUB” in red ink on the cap and “M40” in red ink on the body, containing white and whitish pellets. Capsule length: 20 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)

Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over and adults when remedial measures alone prove insufficient.

Treatment must be initiated and supervised by a physician specialised in the treatment of ADHD such as an expert paediatrician, a child and adolescent psychiatrist or a psychiatrist.

Special diagnostic considerations for ADHD in children

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 electroencephalogram (EEG). Learning may or may not be impaired.

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.

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.

Special diagnostic considerations for ADHD in adults

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.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test.

Adults with ADHD have symptom patterns characterised by, restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD. Diagnosis in adults should include a

structured patient interview to determine current symptoms. The pre-existence of childhood ADHD is required and has to be determined retrospectively (by patients' records or if not available by appropriate and structured interviews). Third-party corroboration is desirable and Meflynate XL should not be initiated when the verification of childhood ADHD symptoms is uncertain Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment and diagnosis should include moderate to severe functional impairment in at least 2 settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician specialised in the treatment of ADHD such as an expert paediatrician, a child and adolescent psychiatrist or a psychiatrist.

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/unexplained death and accurate recording of pre-treatment height (in children only) and weight on a growth chart (see sections 4.3 and 4.4).

Ongoing monitoring

Growth (in children/adolescents), weight (in adults), 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 (children), weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- Weight should be recorded in adults regularly;
- 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. Adult titration may be initiated with 20 mg.

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

The specific galenics of Meflynate XL simulate twice daily administration of an immediate-release methylphenidate formulation. About 50% of the total amount of the active substance is available in unretarded, immediate-release form, while the remaining 50% are released after approximately 4 hours.

If symptoms do not improve after dose titration over a period of one month, the medicinal product should be discontinued.

If symptoms worsen or other adverse effects occur, the dose should be reduced or, if necessary, the medicinal product discontinued.

The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed. Meflynate XL should not be taken too late in the morning as it may cause disturbances in sleep.

The dose should be titrated individually, in accordance with the clinical needs and patient’s responses. For the treatment of ADHD, the time of methylphenidate intake should be chosen in such a way that the effect concurs with the time of the largest school (in children) and social problems as well as behavioural abnormalities of the patient.

Children (6 years and over)

Meflynate XL should be taken once daily in the morning. The recommended starting dose of Meflynate XL is 20 mg. When in the judgment of the clinician a lower initial dose is appropriate, the patient should begin treatment with 10 mg, alternatively it is recommended to start with conventional short-acting methylphenidate 10 mg and continuously increase according to the

recommendation for this formulation. The maximum daily dosage of methylphenidate is 60 mg.

If the effect of the medicinal product wears off too early in the late afternoon, disturbed behaviour and/or inability to go to sleep may recur. A small dose of an immediate-release methylphenidate late in the day may help to solve this problem.

In that case, it could be considered that adequate symptom control might be achieved with a twice daily immediate-release methylphenidate regimen.

The pros and cons of a small evening dose of immediate-release methylphenidate versus disturbances in falling asleep should be considered.

Treatment should not continue with long-acting methylphenidate if an additional late dose of immediate-release methylphenidate is required, unless it is known that the same extra dose was also required for breakfast/lunchtime.

Adults

Meflynate XL should be taken once daily usually in the morning.

The time of the intake may be adapted according to the patient's individual needs, but intake should not be too late in the morning in order to prevent sleep disturbances. The dose should be titrated individually. Dose titration in adults can be started at 20 mg. Only the modified-release formulation of methylphenidate should be used for the treatment of ADHD in adults. A maximum daily dose of 80 mg should not be exceeded.

Patients new to methylphenidate (see section 5.1)

The recommended starting dose of Meflynate XL in patients who are not currently taking methylphenidate is 20 mg once daily. Meflynate XL dose may be adjusted at weekly intervals in 20 mg increments for adults. For lower doses or smaller increments, other strengths of Meflynate XL or other methylphenidate-containing medicinal products are available.

Patients transitioning from childhood methylphenidate treatment to adulthood

Treatment may be continued with the same daily dose. If the patient was previously treated with an immediate-release formulation, a conversion to an appropriate recommended dose of Meflynate XL should be made (see below "Switching patient's treatment to Meflynate XL").

Periodic assessment of the treatment in ADHD

Meflynate XL should be discontinued periodically to assess the patient's condition. Improvement may continue when the medicinal product is temporarily or permanently discontinued. Treatment may be restarted as appropriate to control the symptoms of ADHD. Medicinal product treatment should not, and need not, be indefinite. When used in children with ADHD, treatment can usually be discontinued during or after puberty.

Switching patient's treatment to Meflynate XL

Meflynate XL, administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of immediate-release methylphenidate administered twice daily.

In patients taking methylphenidate twice daily, the recommended dose of Meflynate XL should be equal to the total daily dose of the immediate-release formulation not exceeding a total dose of 60 mg in children and 80 mg in adults. The recommended dose of Meflynate XL for patients switched from an immediate-release formulation or a modified-release formulation to Meflynate XL is as shown in table 1:

Table 1

Previous methylphenidate dose	**Recommended Meflynate XL dose**
5 mg methylphenidate twice daily	10 mg modified-release methylphenidate once daily
10 mg methylphenidate twice daily	20 mg modified-release methylphenidate once daily
15 mg methylphenidate twice daily	30 mg modified-release methylphenidate once daily
20 mg methylphenidate twice daily	40 mg modified-release methylphenidate once daily
30 mg methylphenidate twice daily	60 mg modified-release methylphenidate once daily

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. Meflynate XL dose for treatment of ADHD may be adjusted at weekly intervals in 10 mg increments.

The maximum daily dose of methylphenidate is 60 mg for treatment of ADHD in children and 80 mg for treatment of ADHD in adults.

<u>Long-term (more than 12 months) use</u>

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials in children and adolescents. The long-term safety of methylphenidate has not been systematically evaluated in controlled clinical trials in adults. Methylphenidate treatment should not and need not, be indefinite. In children and adolescents with ADHD methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in patients 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 patient's condition (for children, preferably 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 dose adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dose should be reduced or discontinued.

Special patient groups

Elderly

Methylphenidate should not be used in the elderly. Safety and efficacy in this age group has not been established. The modified-release formulation has not been evaluated in ADHD in patients older than 60 years.

Hepatic impairment

Methylphenidate has not been investigated 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.

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

Meflynate XL (modified-release hard capsules) is for oral use once daily in the morning.

Meflynate XL may be administered with or without food. The capsules may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of food (see specific instructions below).

The capsules of Meflynate XL must not be crushed, chewed, or divided.

Administration by sprinkling capsule contents on food

For ease of intake, the modified-release capsules may be carefully opened and the pellets sprinkled over soft food (e.g. apple sauce). The food should not be warmed because this could affect the modified-release properties of this formulation. The mixture of medicinal product and food should be consumed immediately in its entirety. The medicinal product and food mixture should not be stored for future use. The pellets sprinkled over food (e.g. apple sauce) should not be chewed or crushed.

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 medicinal products, 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 I) Bipolar (affective) Disorder (that is not well-controlled)

- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina pectoris, 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 patients with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the symptoms (for children in relation to age.)

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

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

Methylphenidate treatment should not and need not, be indefinite. In children and adolescents with ADHD 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 (children), weight, appetite, and 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 patients 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 patient's condition (for children preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in the elderly

Methylphenidate must not be used in the elderly. Safety and efficacy of Meflynate XL has not been evaluated in ADHD in patients older than 60 years.

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 stimulants 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. Changes in diastolic and systolic blood pressure values were also observed in clinical trial data from adults ADHD patients. However, these changes were smaller compared to children and adolescents (around 2–3 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. See section 5.1 under subheading “ADHD in adults”.

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 cardiac 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 cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulants are not recommended in patients 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.

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. Prior to initiating treatment with methylphenidate the patient should be assessed with regard to pre-existing psychiatric disorders and a family history thereof should be established (see section 4.2). In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate therapy 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 patients without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses (see section 4.8). 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 (see section 4.8). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients 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 stimulants 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 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.**

<u>Growth and weight loss</u>

Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. Weight decrease has been reported with methylphenidate treatment in adults (see section 4.8).

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

Growth should be monitored in children 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. In adults, weight should be regularly monitored.

<u>Seizures</u>

Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient 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 dose 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.

Choice of methylphenidate formulation

The choice of formulation of methylphenidate-containing medicinal product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect. For the treatment of ADHD in adults, only the Meflynate XL modified-release hard capsules formulation should be used.

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. Patients requiring long-term therapy should be carefully monitored and periodically complete and differential blood counts as well as platelet counts should be performed. 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.

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.

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.

Drug screening

Methylphenidate may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Effects in case of misuse as doping agent
Use of Meflynate XL can lead to positive results in doping tests.
Misuse of Meflynate XL for doping purposes may pose a risk to health.

Excipients

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other medicinal products, 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 dose of these medicinal products already being taken and establish plasma concentrations of medicinal products (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive medicinal products

Methylphenidate may decrease the effectiveness of medicinal products used to treat hypertension.

Use with medicinal products that elevate blood pressure

Caution is advised in patients being treated with methylphenidate with any other medicinal product that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

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

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive medicinal product, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment. In case of very high alcohol concentrations, the kinetic profile may change towards a more immediate-release-like pattern.

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 medicinal products

Caution is recommended when administering methylphenidate with dopaminergic medicinal products, 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.

Antacids

Concomitant use of antacids is expected to lead to a considerably lower absorption of methylphenidate.

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 case reports.

Studies in animals have only 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 breast-fed 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. In animal studies, no clinically relevant effects on fertility were observed.

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 (see section 4.8). 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 Meflynate XL and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with Meflynate XL and the other methylphenidate formulations frequencies were different, the highest frequency of both databases was used.

The table is based on data collected in children, adolescents and adults.

Frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	Undesirable effects					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis	Gastroenteritis			
Blood and lymphatic system disorders					Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus (1), rashes, and eruptions (1)			
Metabolism and nutrition disorders (1)	Decreased appetite (2)	Anorexia, moderately reduced weight and height gain during prolonged				

System Organ Class	Undesirable effects					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
		use in children (1), weight decrease in adults (2)				
Psychiatric disorders (1)	Insomnia, nervousness	Affect lability, aggression (1), agitation (1), anxiety (1), depression (1), irritability, abnormal behaviour, restlessness (2), sleep disorder (2), libido decreased (3), panic attack (3), stress (3), bruxism (3)	Psychotic disorders (1), auditory, visual, and tactile hallucinations (1), anger, suicidal ideation (1), mood altered, mood swings, tearfulness, tics (1), worsening of pre-existing tics or Tourette's syndrome (1), hypervigilance, tension (3)	Mania (1), disorientation, libido disorder, obsessive-compulsive disorder (including trichotillomania and dermatillomania)	Suicidal attempt (including completed suicide) (1), transient depressed mood (1), abnormal thinking, apathy	Delusions (1), thought disturbances (1), confusional state, dependence, logorrhoea. Cases of abuse and dependence have been described, more often with immediate-release formulations
Nervous system disorders	Headache	Tremor (2), somnolence, dizziness, dyskinesia, psychomotor hyperactivity, somnolence	Sedation, akathisia (3)		Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly	Cerebrovascular disorders (1) (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis,

System Organ Class	Undesirable effects					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
					documented and in most of these cases, patients were also receiving other medicinal products, so the role of methylphenidate is unclear)	cerebral occlusion), grand mal convulsions (1), migraine, dysphemia
Eye disorders			Diplopia, blurred vision, dry eye (4)	Difficulties in visual accommodation, mydriasis, visual disturbance		Increased intraocular pressure, glaucoma
Cardiac disorders		Arrhythmia, palpitations, tachycardia (2)	Chest pain	Angina pectoris	Cardiac arrest, myocardial infarction	Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles
Vascular disorders (1)		Hypertension, peripheral coldness (2)			Cerebral arteritis and/or occlusion, Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders		Cough, pharyngolaryngeal pain, dyspnoea (2)				Epistaxis

System Organ Class	Undesirable effects					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Gastrointestinal disorders	Nausea (2), dry mouth (2)	Abdominal pain, diarrhoea, stomach discomfort, vomiting, dyspepsia (3), toothache (3) (these effects usually occur at the start of treatment and may be alleviated by concomitant intake of food)	Constipation			
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function including hepatic coma	
Skin and subcutaneous tissue disorders		Hyperhidrosis (2), alopecia, pruritus, rash, urticaria	Angioneurotic oedema, bullous conditions, exfoliative conditions	Macular rash, erythema	Erythema multiforme, exfoliative dermatitis, fixed drug eruption	
Musculoskeletal and connective tissue disorders		Arthralgia	Myalgia, muscle twitching, muscle tightness (3)		Muscle cramps	Trismus (3)
Renal and urinary disorders			Haematuria			Incontinence
Reproductive system and breast				Gynaecomastia		Erectile dysfunction, Priapism,

System Organ Class	Undesirable effects					
	Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
disorders						erection increased and prolonged erection
General disorders and administration site conditions		Pyrexia, growth retardation during prolonged use in children (1), feeling jittery (3), fatigue (2), thirst (3)			Sudden cardiac death (1)	Chest discomfort, hyperpyrexia
Investigations		Changes in blood pressure and heart rate (usually an increase) (1), weight decreased (1)	Cardiac murmur (1), hepatic enzyme increased		Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal	

(1) See section 4.4.
(2) ADR from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents.
(3) Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies.
(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.

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 the Yellow Card Scheme Website: 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 overdose.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation 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 be given before performing gastric lavage.

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: Psychoanaleptics, psychostimulants agents used for ADHD and nootropics, centrally acting sympathomimetics, ATC code: N06BA04

Mechanism of action

Methylphenidate, the active substance of Meflynate XL, is a psychostimulant with more prominent effects on central nervous than on motor activities. Chemically, it is an alkaline ester of phenyl acetic acid. The molecule contains the phenylethylamine backbone that is considered responsible for the amphetamine-like effects. Methylphenidate contains two chiral centres and therefore has four stereoisomers. The pharmacodynamically active configuration is the threo-form. The d-isomer is pharmacologically more active than the l-isomer.

In animal studies methylphenidate exerts an indirect sympathomimetic effect by release of noradrenaline from intraneuronal stores of adrenergic neurons and inhibition of its reuptake. Dose-dependently, i.e. with increasing concentration in the central nervous system, methylphenidate also releases dopamine and inhibits its reuptake. In contrast to amphetamine, catecholamines are not released by methylphenidate in animals pre-treated with reserpine. This means that reserpine inhibits methylphenidate-induced stereotypies.

Its mode of action in man is not completely understood but its stimulant 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 is not clearly established.

The indirect sympathomimetic effect of methylphenidate in humans can lead to increase in blood pressure, acceleration of heart rate and decrease in bronchial muscle tone. These effects are usually not very marked. The centrally stimulating effect can be seen e.g. in an enhancement of concentration, performance and decision making, psychophysical activity as well as suppression of tiredness and physical exhaustion. Misuse in particular may lead to misjudgement of the limits of capacity and even to the breakdown of physiological functions and to death at overdosing. Methylphenidate can suppress appetite and can, at high doses, cause an increase in body temperature. Behavioural stereotypies can also be elicited by high doses or prolonged use.

ADHD in adults

Methylphenidate was evaluated in a combined short-term and long-term core study consisting of three periods (Period 1= 9 weeks short-term treatment, Period 2= 5 weeks open label treatment with methylphenidate without placebo

control; Period 3= randomised withdrawal phase). This core study was followed by a 26-week open label extension study.

The core study was a randomised, double-blind, placebo-controlled, multicentre study in the treatment of 725 adult patients (395 male and 330 female) diagnosed with ADHD according to DSM-IV ADHD criteria. The study was designed to:

1) Confirm efficacy and safety of methylphenidate in adults (18 to 60 years old) in a 9-week, double-blind, randomised, placebo-controlled, parallel group period (Period 1) consisting of a 3-week titration stage followed by a 6-week fixed dose stage (40, 60, 80 mg/day or placebo). Subsequently patients were re-titrated to their optimal dose of methylphenidate (40, 60 or 80 mg/day) over a 5 week period (Period 2).

2) Evaluate the maintenance of effect of methylphenidate in adults with ADHD in a 6-month, double-blind, randomised, withdrawal study (period 3).

Efficacy was assessed using the DSM-IV ADHD rating scale (DSM-IV ADHD RS) for symptomatic control and Sheehan Disability Score (SDS) for functional improvement as improvement in respective total scores from baseline to the end of the first period. All dose levels of methylphenidate showed significantly greater symptom control ($p<0.0001$ for all dose levels) compared to placebo as measured by a reduction in DSM-IV ADHD RS total score. All doses of methylphenidate showed significantly greater functional improvement ($p=0.0003$ at 40 mg, $p=0.0176$ at 60 mg, $p<0.0001$ at 80 mg) compared to placebo as measured by improvement in SDS total score (see Table 2).

Clinical efficacy was demonstrated in all three methylphenidate dose levels using physician rated scales [Clinical Global Impression-Improvement (CGI-I) and Clinical Global Improvement- Severity (CGI-S)], self-rated scales [Adult Self-Rating Scale (ASRS)] and observer-rated scales [Conners' Adult ADHD Rating Scale Observer Short Version (CAARS O:S)]. The results were in favour of methylphenidate over placebo across all assessments in Period 1.

Table 2 Analysis of improvement from baseline 1 to end of Period 1 in DSM IV ADHD RS total score and SDS total score by treatment / (LOCF*) for Period 1

		Methylphenidate 40 mg	Methylphenidate 60 mg	Methylphenidate 80 mg	Placebo
Improvement in DSM- IV ADHD RS from baseline	N	160	155	156	161
	LS mean*	15.45	14.71	16.36	9.35
	p- value****	<0.0001	<0.0001	<0.0001	
	Significance level	0.0167	0.0208	0.0313	

Improvement in SDS total score from baseline	N	151	146	148	152
	LS mean	5.89	4.9	6.47	3.03
	p-value****	0.0003	0.0176	<0.0001	
	Significance level***	0.0167	0.0208	0.0313	

* LOCF – Last Observation Carried Forward using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1, **LS mean – Least Square mean improvement from Analysis of Covariance (ANCOVA) model with treatment group and centre as factors and baseline DSM-IV ADHD RS total score and SDS total score as covariate, ***Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure, ****p-value refers to comparison against placebo.

Maintenance of effect of methylphenidate was evaluated by measuring the percentage of treatment failure in methylphenidate compared to the placebo group at the end of a 6-month maintenance period (see Table 3). Once the methylphenidate dose was optimised in Period 2, approximately 79% of patients continued to maintain disease control for a period of at least 6 months (p <0.0001 vs. placebo). An odds ratio of 0.3 suggested that patients treated with placebo had a 3 times higher chance of becoming a treatment failure compared to methylphenidate.

Table 3 Percentage of treatment failures during Period 3

			All Ritalin LA vs placebo	
	All methylphenidate N=352 n (%)	Placebo N=115 n (%)	Odds ratio (95% CI)	P-value* (significance level**)
Treatment failure	75 (21,3)	57 (49,6)	0,3 (0,2, 0,4)	<0,0001 (0,0500)
Not treatment failure	277 (78,7)	58 (50,4)		

* Two-sided p-value based on comparison between each methylphenidate group and placebo using the logistic regression model.

**Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure

Patients who entered Period 3 had completed a total of between 5-14 weeks of methylphenidate treatment in Periods 1 and 2. Patients then assigned to placebo in Period 3 did not experience increased signs of withdrawal and rebound compared to patients who continued on methylphenidate treatment.

During short-term treatment both females and males had a statistically better improvement of DSM-IV ADHD RS compared to placebo in all methylphenidate dose groups. For men best numerical improvement of the score was achieved with methylphenidate 80 mg, whereas for women best improvement was reached in the lowest dose group methylphenidate 40 mg. This trend was not significant and not seen during long-term treatment. A slightly higher incidence of AEs was observed in females compared to males; however, in general, a similar safety profile was demonstrated for males and females. Therefore, the dose should be titrated individually (maximal possible dose 80 mg/d). The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

The 26-week open label extension of the core study of methylphenidate in 298 adult patients with ADHD showed long-term safety of methylphenidate. Combining the continuous exposure to methylphenidate of all patients treated in the core and the extension studies, a total of 354 patients continuously received methylphenidate for >6 months and 136 patients for >12 months.

The safety profile of methylphenidate did not change with the longer duration of treatment of adult ADHD patients, as observed during this extension study. The AE profile seen in the extension patients was similar to that observed in the core study. No unexpected SAEs were observed in this extension study and also most of the observed AEs were expected.

The total frequency of AE and some specific AE increased with exposure time. Decreased weight occurred in 0.7% (≤2 months), 5.6% (>6 months) and 7.4% (>12 months) of the patients. In period 3 there was a significant weight decrease ≥7% in 13.8% of the patients (in the 6-months maintenance period) compared to baseline. Insomnia/initial insomnia/sleep disorder increased with long-term treatment >12 months. Incidence of depressed mood slightly increased over time (4.8% for the periods of <2 months, 4.5% for >6 months and 6.6% >12 months) whereas depression decreased over time (0% in >12 months). Incidence of tachycardia and palpitations slightly increased with long-term exposure (tachycardia: 4.8% with exposure <2 months and 6.6% with exposure >12 months; palpitations 6.9% with exposure <2 months and 9.6% with exposure >12 months). Also incidence of high blood pressure slightly increased with long-term exposure; from 2.1% with exposure <2 months to 5.1% with exposure >12 months. Mean change in HR increased from 2.4 bpm (exposure <2 months) to 4.9 resp. 4.8 bpm (exposure >6 months resp. exposure >12 months).

Tachycardia: at baseline, the percentage of patients with a heart rate >100 bpm was very small (0.4% in the methylphenidate group and 0.6% in the placebo group). Whereas with methylphenidate 11.3% of those with a normal baseline heart rate developed a heart rate >100 bpm in at least one of the visits during short-term treatment (and only 2.2% in the placebo group). During long-term treatment 8.6% compared to 3.4% (methylphenidate vs. placebo) of those with

a normal baseline heart rate developed a heart rate >100 bpm in at least one of the visits.

5.2 Pharmacokinetic properties

Meflynate XL is a racemate consisting of a 1:1 mixture of d-methylphenidate and l-methylphenidate.

Absorption
Following oral administration of methylphenidate (modified-release hard capsules) to children diagnosed with ADHD and adults, methylphenidate is rapidly absorbed and produces a bimodal plasma concentration-time profile (i.e. two distinct peaks approximately four hours apart). The relative bioavailability of modified-release methylphenidate given once daily in children and adults is comparable to the same total dose of immediate-release methylphenidate given twice a day.

The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for modified-release methylphenidate given once daily compared to immediate-release methylphenidate given twice a day.

Food effects
Meflynate XL modified-release hard capsules may be administered with or without food. There were no differences in the bioavailability of modified-release methylphenidate when administered with either a high fat breakfast or apple sauce compared to administration in the fasting conditions. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the modified-release hard capsule, the contents may be sprinkled on soft food (such as apple sauce) and administered immediately (see section 4.2).

Distribution
In the blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Methylphenidate and its metabolites have a low plasma protein-binding (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.
Methylphenidate easily passes the blood brain barrier.

Biotransformation
Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive. Methylphenidate is mainly metabolised to α-phenyl-2-piperidine acetic acid (ritalinic acid). Peak plasma concentrations of α-phenyl-2-piperidine acetic acid are attained about 2 hours after administration and are 30-50 times higher than those of the unchanged substance. The half-life of α-phenyl-2-piperidine acetic acid is about twice that of methylphenidate, and its mean systemic clearance is 0.17 l/h/kg. Accumulation may therefore be possible in patients with renal insufficiency. Since α-phenyl-2-piperidine acetic acid has

little or no pharmacologic activity, this plays a subordinate therapeutic role. Only small amounts of hydroxylated metabolites (e.g. hydroxymethylphenidate and hydroxyic 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. After oral administration, 78-97% of the dose administered is excreted in the urine and 1-3% in the faeces in the form of metabolites within 48 to 96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as α-phenyl-2-piperidine acetic acid (60-86%), probably pH independent.

There are no apparent differences in the pharmacokinetic of methylphenidate between children with hyperkinetic disorders/ADHD and healthy adult volunteers. Elimination data from patients with normal renal function suggest that renal excretion of unchanged methylphenidate would hardly be diminished in the presence of impaired renal function. However, renal excretion of the main metabolite α-phenyl-2-piperidine acetic acid may be reduced.

5.3 Preclinical safety data

Methylphenidate is considered as potentially teratogenic in rabbits. Spina bifida with deformities of the back limbs was observed in two separate litters at a dose of 200 mg/kg/day. On an mg/kg base, this dose was approximately 116 times higher than the maximum recommended dose in humans (MRHD) of 60 mg in children and adolescents. At 200 mg/kg/day, the systemic exposure (AUC) of dl-methylphenidate in rabbits was 5.1 times the extrapolated MRHD following the administration of 60 mg (in children and adolescents). Exposure at the next lower dose for which spina bifida was not observed amounted to 0.72 times the extrapolated MRHD in children and adolescents. In a second study using the high dose of 300 mg/kg, which is considered as maternally toxic, no case of spina bifida was observed in 12 litters with 92 live foetuses. At 300 mg/kg, the systemic exposure (AUC) was 7.5 times higher than extrapolated maximum human therapeutic exposure in children and adolescents.

Genotoxicity studies do not reveal any special hazard for humans.

Repeated oral administration of methylphenidate to young rats identified decreased spontaneous locomotor activity at 50 mg/kg/day (29-fold higher than the MRHD in children and adolescents), due to an exaggerated pharmacological activity of methylphenidate. Exposure (AUC) at this dose was 15.1-fold higher than the extrapolated maximum human therapeutic

exposure at the maximum recommended dose of 60 mg in children and adolescents. A deficit in the acquisition of a specific learning task was also observed, only in females and at the highest dose of 100 mg/kg/day (58-fold higher than the MRHD in children and adolescents). At this dose, the systemic exposure amounted to 40.1 times the extrapolated maximum human exposure. The clinical relevance of these findings is unknown.

Unlike these preclinical findings, long-term administration of methylphenidate in children with ADHD is well tolerated and improves the school performance. Thus, the clinical experience does not suggest that these learning and behavioural results in rats are clinically relevant.

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

Capsule contents
Ammonio methacrylate copolymer (type B)
Methacrylic acid - methyl methacrylate copolymer (1:1)
Povidone 30
Sugar spheres (containing sucrose and maize starch)
Talc
Triethyl citrate

Capsule shell
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172).

Printing ink

Potassium hydroxide
Propylene glycol
Red iron oxide (E172)
Shellac glaze
Strong ammonia solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Child resistant blisters (Aclar/PVC//Al/PET) boxed in cardboard cartons.

Pack sizes:

28, 30, 50, 54, 56, 60, 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Flynn Pharma Limited

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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