SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Addepta XL 30 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release hard capsule contains 30 mg methylphenidate hydrochloride equivalent to 25.95 mg methylphenidate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Opaque oblong hard capsule with yellow cap and white body imprinted “30” with black ink on body filled with white to off-white spherical pellets. Capsule length: 18 mm, size 2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children from 6 years of age 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-IV criteria or the guidelines in ICD-10 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 ADHD and the decision to use the medicinal product 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. Methylphenidate should always be used in this way according to the licensed indication and according to prescribing/diagnostic guidelines.

4.2 Posology and method of administration

Posology

Addepta XL consists of an immediate release component (30% of the dose) and a modified release component (70% of the dose). Hence Addepta XL 10 mg yields an immediate-release dose of 3 mg and an extended release dose of 7 mg methylphenidate hydrochloride. The extended-release portion of each dose is designed to maintain a treatment response through the afternoon without the need for a midday dose. It is designed to deliver therapeutic plasma levels for a period of approximately 8 hours, which is consistent with the school day rather than the whole day (see section 5.2). For example, 20 mg of Addepta XL is intended to take the place of 10 mg at breakfast and 10 mg at lunchtime of immediate release methylphenidate hydrochloride.

Paediatric population (Children (aged 6 years and over) and adolescents):

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 comorbid 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, weight, 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. This is usually accomplished by using an immediate-release formulation divided into multiple doses. The recommended initial dose is 5 mg once or twice daily (for example for breakfast and lunch). If necessary, the daily dose may be increased weekly in increments of 5 - 10 mg, depending on the tolerability and the observed degree of effectiveness. Instead of twice daily administration of an immediate release methylphenidate hydrochloride 5 mg formulation, Addepta XL 10 mg may be used from the beginning of treatment if the treating physician determines that twice daily dosing is appropriate at baseline but twice daily dosing is not feasible.

The maximum daily dose of methylphenidate hydrochloride is 60 mg.

For doses not realisable/practicable with this strength, other strengths of this medicinal product and other methylphenidate-containing products are available.

Patients currently using methylphenidate

Patients established on an immediate release methylphenidate hydrochloride formulation may be switched to the milligram equivalent daily dose of Addepta XL.

Addepta XL should be given in the morning before breakfast.

Addepta XL should not be taken too late in the morning as it may cause disturbances in sleep. If the effect of the medicinal product wears off too early in the late afternoon or evening, disturbed behaviour and/or inability to go to sleep may recur. A small dose of 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 a conventional immediate-release regimen at equivalent breakfast/lunchtime dose. The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed.

Long-term (more than 12 months) use in children (>6 years of age) and adolescents (<18 years of age)

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials in children and adolescents. Methylphenidate treatment should not and need not, be indefinite. 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 medicinal product for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

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.

Adults

Addepta XL is not approved for the treatment of adults with ADHD. Safety and efficacy have not been demonstrated in this age group.

Special populations

Elderly

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

Children under 6 years of age

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

Method of administration

For oral use.

The capsules may be swallowed whole with the aid of liquids, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of soft food (e.g. applesauce) and given immediately, and not stored for future use. Drinking some fluids, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed.

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 substances, 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

Addepta XL 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 child's symptoms in relation to the child's age.

Long-term use (more than 12 months)

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials in children and adolescents. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4 for cardiovascular status, growth (children), weight, 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 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 medicinal product is either temporarily or permanently discontinued.

Use in adults

Addepta XL is not licensed for the treatment of adults with ADHD. Safety and efficacy of Addepta XL has not been demonstrated in this age group.

Use in the elderly

Addepta XL must not be used in elderly patients. Safety and efficacy have not been established in this age group.

Use in children under 6 years of age

Addepta XL should not be used in children under the age of 6 years. Safety and efficacy of methylphenidate in this age group have 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 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, stimulant products 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 medicine.

Misuse and cardiovascular events

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

Cerebrovascular disorders

See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischaemia 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 stimulants. 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 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. 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.

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 month or every visit.**

Forms of bipolar disorders

Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above 'Psychiatric disorders' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Growth

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

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.

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 of the patients for tics or Tourette's syndrome 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.**

Seizures

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.

Renal or hepatic insufficiency

There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects

The long-term safety of treatment with methylphenidate is not fully known. In the event of leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Priapism

Prolonged and painful erections have been reported in association with methylphenidate medicinal 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.

Drug screening

This methylphenidate-containing medicinal product may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered medicinal products. 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. phenobarbitol, 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 substance plasma concentrations (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 active substances 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 products, 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)

Serious adverse events, including sudden death, have been reported with concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic substances

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

Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Fertility, pregnancy and lactation

Pregnancy

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. 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. If the ADRs with (Invented name) and the other methylphenidate formulations frequencies were different, the highest frequency of both databases was used.

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)

Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Very rare Not known	Leukopenia, thrombocytopenia, anaemia, thrombocytopenic purpura Pancytopenia
Immune system disorders	
Uncommon	Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rashes and eruptions
*Metabolism and nutrition disorders**	
Common	Anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*
*Psychiatric disorders**	
Very common Common	Insomnia, nervousness 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* or worsening of pre-existing tics of Tourette's syndrome*, hypervigilance, sleep disorder
Rare Very rare Not known	Mania*, disorientation, libido disorder Suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviour, over-focussing Delusions*, thought disturbances*, confusional state, dependence, logorrhoea
Cases of abuse and dependence have been described, more often with immediate-release formulations	
Nervous system disorders	

Very common Common Uncommon Very rare Not known	Headache Dizziness, dyskinesia, psychomotor hyperactivity, somnolence Sedation, tremor Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS; reports were poorly documented and in most of cases, patients were also receiving other substances, so the role of methylphenidate is unclear) Cerebrovascular disorders* (including vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral occlusion and cerebrovascular accidents), grand mal convulsions*, migraine
Eye disorders	
Uncommon Rare	Diplopia, blurred vision Difficulties in visual accommodation, mydriasis, visual disturbance
Cardiac disorders	
Common Uncommon Rare Very rare Not known	Arrhythmia, tachycardia**, palpitations Chest pain Angina pectoris Cardiac arrest, myocardial infarction Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles
*Vascular disorders**	
Common Very rare	Hypertension Cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common Uncommon Not Known	Cough, pharyngolaryngeal pain dyspnoea Epistaxis
Gastrointestinal disorders	
Common Uncommon	Abdominal pain, diarrhoea, nausea, stomach discomfort, vomiting, dry mouth Constipation
Hepatobiliary disorders	
Uncommon Very rare	Hepatic enzyme elevations Abnormal liver function including

	hepatic coma
Skin and subcutaneous tissue disorders	
Common Uncommon Rare Very rare	Alopecia, pruritus, rash, urticaria Angioneurotic oedema, bullous conditions, exfoliative conditions Hyperhidrosis, macular rash, erythema Erythema multiforme, exfoliative dermatitis, fixed drug eruption
Musculoskeletal and connective tissue disorders	
Common Uncommon Very rare Not known	Arthralgia Myalgia, muscle twitching Muscle cramps Trismus
Renal and urinary disorders	
Uncommon	Haematuria
Not known	Incontinence
Reproductive system and breast disorders	
Rare Not known	Gynaecomastia Priapism, erection increased, prolonged erection, erectile dysfunction
General disorders and administration site conditions	
Common Uncommon Very rare Not known	Pyrexia, growth retardation during prolonged use in children* Chest pain, fatigue Sudden cardiac death* Chest discomfort, hyperpyrexia
Investigations	
Common Uncommon Very rare	Changes in blood pressure and heart rate (usually an increase)*, weight decreased* Cardiac murmur*, hepatic enzymes increased Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

* See section 4.4.

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 and 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.

Symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate 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

Addepta XL 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 cortical stimulation and possibly to stimulation of the reticular activating system.

In a pivotal study 318 subjects aged between 6 and 12 years received at least one dose of study medication out of 327 subjects randomized. Scores for the IOWA Conner's rating, the primary efficacy endpoint assessed by teachers during the school day, showed the following results for the per protocol population (279 patients treated for 21 days):

	Placebo (N=39)[a]	Immediate Release Methylphenidate (N=120)[b]	Modified-release Methylphenidate (N=120)
Baseline Mean (SD)	6.0 (3.64)	6.1 (3.74)	5.8 (3.59)
Day 21/Withdrawal			
LS Mean (SE)	7.7 (0.50)	4.3 (0.29)	4.5 (0.29)
95% CI	6.69, 8.66	3.71, 4.84	3.98, 51.0
Difference from Placebo	-	-3.4	-3.1
95% CI for the difference	-	-4.53, -2.26	-4.26, -2.00
P-value[c]	-	<0.001	<0.001
Difference from MIR	-		-0.3
97.5% lower CI bound for the difference	-		-1.06
[a] N=38 at Day 7; [b] N=118 at Day 7; [c] Treatment groups have been compared using ANCOVA, with effects for treatment and baseline as covariates			

In contrast to these results for the primary efficacy measure, differences between the modified-release

methylphenidate and immediate release methylphenidate groups were observed for the Parent IOWA Conner's secondary efficacy variable. This was based on assessments later in the evening, suggesting that there is some loss of efficacy of modified-release methylphenidate late in the day relative to twice daily immediate release methylphenidate. See also section 5.2. and section 4.2.

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. It is thought to block the re-uptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture of the d- and l-threo enantiomers of methylphenidate. The d-enantiomer is more pharmacologically active than the l-enantiomer.

5.2 Pharmacokinetic properties

Absorption

Addepta XL has a plasma profile showing two phases of active substance release, with a sharp, initial, upward slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline.

Peak plasma concentrations of approximately 40 nmol/litre (11 ng/ml) are attained, on average, 1-2 hours after administration of 0.30 mg/kg. The peak plasma concentrations, however, show considerable intersubject variability.

The range of concentrations at 1.5 hours was 3.2 – 13.3 ng/ml with a mean of 7.7 ng/ml. The second phase of release resulted in a second maximum observed concentration in most subjects at 4.5 hours after dosing, with the observed concentrations ranging from 4.9 – 15.5 ng/ml with a mean of 8.2 ng/ml. Administration of an extended release formulation at breakfast instead of two immediate release formulation tablets (breakfast and lunch) may reduce the pre-lunch trough and post lunch peak of methylphenidate, and plasma levels may be lower after the end of the school day. Clinical trial data suggest that the different pharmacokinetic profiles may result in a different pattern of behaviour and symptom control during the day for some patients compared with a conventional immediate release methylphenidate regimen. In particular there may be some reduction of symptom control in the late afternoon and early evening (see section 5.1). These differences should be taken into consideration when assessing their individual requirements.

The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, is proportional to the dose.

Food effects

Ingestion together with food with a high fat content delays its absorption (T_{max}) by approximately one hour and increases the maximum concentration (C_{max}) by approximately 30% and the amount absorbed (AUC) by approximately 17%.

Sprinkle administration

The C_{max} T_{max} and AUC of the sprinkled contents of the Addepta XL capsule are similar (bioequivalent) to the intact capsule. Addepta XL may, therefore, be administered either as an intact capsule, or the capsule may be opened and the contents swallowed, without chewing, immediately after sprinkling onto applesauce or other similar soft food.

Age

The Pharmacokinetics of Addepta XL have not been studied in children younger than 7 years of age.

Availability, systemic

Owing to extensive first-pass metabolism its systemic availability amounts to approximately 30% (11-51%) of 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-building rate (10-33%). The apparent distribution has been calculated as 13.1 litres/kg.

Elimination

Methylphenidate is eliminated from the plasma with a mean half-life 2 hours, and the calculated mean systemic clearance is 10 litres/h/kg.

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.

The bulk of the dose is excreted in the urine as 2-phenyl-2-piperidyl acetic acid (PPAA, 60-86%).

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

Capsule contents

Microcrystalline cellulose

Hypromellose

Ethylcellulose

Hydroxypropylcellulose

Dibutyl sebacate

Povidone

Talc (E553b)

Hydrochloric acid (E507-for pH adjustment)

Capsule shell

Hypromellose

Titanium dioxide (E171)

Iron oxide yellow (E172)

Printing ink

Shellac (E904)

Iron oxide black (E172)

Propylene glycol (E1520)

Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with child-resistant PP screw caps containing a desiccant.

Pack size:

28, 30, 50, 60, 100 modified-release hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd

Dashwood House,

69 Old Broad Street,

London, EC2M 1QS,

United Kingdom

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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