SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Exattent XL 60 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 60 mg methylphenidate hydrochloride equivalent to 51.9 mg methylphenidate.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Exattent XL is a hard opaque capsule with orange cap and white body, imprinted with "60" in black ink on the body, filled with white to off-white spherical pellets. Capsule length: 21.70 ± 0.30 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to 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 this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity and the chronicity of the child's symptoms in relation to the child's age. Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to the prescribing/diagnostics guidelines.

4.2 Posology and method of administration

This medicinal product consists of an immediate release component (30% of the dose) and a modified release component (70% of the dose). Hence it yields an immediate-release dose of 18 mg and an extended release dose of 42 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 "Pharmacokinetic properties"). For example, 20 mg of this medicinal product 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, 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 in children 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 normally achieved using an immediate release formulation taken in divided doses. The recommended starting daily dose is 5 mg once daily or twice daily (e.g., at breakfast and lunch), increasing if necessary, by weekly increments of 5-10 mg in the daily dose according to tolerability and degree of efficacy observed. Exattent XL 10 mg once daily may be used in place of immediate release methylphenidate hydrochloride 5 mg twice daily from the beginning of treatment where the treating physician considers that once daily dosing is appropriate from the outset and twice daily treatment administration is impracticable.
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 this medicinal product.
Treatment 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 an immediate-release methylphenidate hydrochloride tablet 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 this medicinal product 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.
This medicinal product should be given in the morning before breakfast.
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 apple sauce and given immediately, and not stored for future use. Drinking some fluids, e.g., water, should follow the intake of the sprinkles with apple sauce. The capsules and the capsule contents must not be crushed or chewed.
<u>Long term (more than 12 months) use in children and adolescents</u>

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically

re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

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

Adults

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

Elderly

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

Children under 6 years of age

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

4.3 Contraindications

Methylphenidate is contra-indicated in patients with:

- 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 following discontinuing those drugs, due to risk of hypertensive crises (see Section 4.5)
- Hyperthyroidism or thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) disorder (that is not well-controlled)
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels)
- Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke.

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age. Long term use (more than 12 months) in children and adolescents

The safety and efficacy of long-term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e., over 12 months) must have careful ongoing monitoring according to the guidance in section 4.2 and 4.4 for cardiovascular status, growth, appetite, development of *de novo* or worsening of preexisting psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued. Use in adults

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

Use in the elderly

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

Use in children under 6 years of age

Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy 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 centile chart at each adjustment of dose and then at least every 6 months.

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

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders
Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had structural cardiac abnormalities or other serious heart problems.

Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

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

Cerebrovascular disorders:

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

Cerebral vasculitis appears to be very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders

Comorbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing psychotic or manic symptoms
In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour
The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency
Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in 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 methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with 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.

<u>Growth</u>

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

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

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6-monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued. 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. 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.

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 comorbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered. Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue

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

Drug screening

This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Choice of methylphenidate formulation

The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

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.

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 drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l-enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors).

When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

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

Use with drugs that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and

cerebrovascular conditions in Section 4.4 Warnings and Precautions for use). Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3 Contraindications).

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

Use with halogenated anaesthetics
There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2agonists (e.g., clonidine)
Serious adverse events, including sudden death, have been reported in 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 drugs
Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extra cellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have only shown reproductive toxicity at maternally toxic doses (see Section 5.3).

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

Breast-feeding

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

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

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

4.7 Effects on ability to drive and use machines

This medicinal product may cause dizziness, drowsiness and visual disturbances including difficulties with accommodations, 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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while under the influence of this medicine.
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post market spontaneous reports with methylphenidate and those, which have been reported with other methylphenidate hydrochloride formulations. If ADRs with methylphenidate and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

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

System Organ Class	**Adverse Drug Reaction**
Infections and infestations	
Common:	nasopharyngitis
Blood and lymphatic system disorders	

Very rare:	anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura
Not known:	pancytopenia
Immune System Disorders	
Uncommon:	hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, 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:	insomnia, nervousness
Common:	anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour, bruxism**
Uncommon:	psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder
Rare:	mania*, disorientation, libido disorder, obsessive-compulsive disorder (including trichotillomania and dermatillomania)
Very rare:	suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy
Not known:	delusions*, thought disturbances*, confusional state, dependence
Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)	
Nervous system disorders	
Very common:	headache
Common:	dizziness, dyskinesia, psychomotor hyperactivity, somnolence
Uncommon:	sedation, tremor
Very rare:	convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit neuroleptic malignant syndrome (NMS; Reports were poorly documented and,

	in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear)
Not known:	cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine, dysphemia

Eye disorders	
Uncommon:	diplopia, blurred vision, dry eye†
Rare:	difficulties in visual accommodation, mydriasis, visual disturbance
Not known:	increased intraocular pressure, glaucoma
Cardiac disorders	
Common:	arrhythmia, tachycardia, palpitations
Uncommon:	chest pain
Rare:	angina pectoris
Very rare:	cardiac arrest, myocardial infarction
Not known:	supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles
Vascular disorders*	
Common:	hypertension
Very rare:	cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	cough, pharyngolaryngeal pain
Uncommon:	dyspnoea
Gastrointestinal disorders	
Common:	abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting, dry mouth
Uncommon:	constipation
Hepatobiliary disorders	
Uncommon:	hepatic enzyme elevations
Very rare:	abnormal liver function, including hepatic coma
Skin and subcutaneous tissue disorders	
Common:	alopecia, pruritus, rash, urticaria
Uncommon:	angioneurotic oedema, bullous conditions, exfoliative conditions
Rare:	hyperhidrosis, macular rash, erythema
Very rare:	erythema multiforme, exfoliative dermatitis, fixed drug eruption
Musculoskeletal and connective tissue disorders	
Common:	arthralgia
Uncommon:	myalgia, muscle twitching
Very rare:	muscle cramps
Not known	trismus**
Renal and urinary disorders	
Uncommon:	haematuria

Not known	incontinence
Reproductive system and breast disorders	
Rare:	gynaecomastia
Not known:	priapism, erection increased and prolonged erection*, erectile dysfunction
General disorders and administration site conditions	
Common:	pyrexia, growth retardation during prolonged use in children*
Uncommon:	chest pain, fatigue
Very rare:	sudden cardiac death*
Not known:	chest discomfort, hyperpyrexia
Investigations	
Common:	changes in blood pressure and heart rate (usually an increase)*, weight decreased
Uncommon:	cardiac murmur*, hepatic enzyme increased
Very rare:	blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

* See Section 4.4 'Special Warnings and precautions for use'
** Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies)
† Frequency derived from adult clinical trials and not on data from trials in children and adolescents; may also be relevant for children and adolescents

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after 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, psychosis, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage.

Treatment consists of appropriate supportive measures.
The patient must be protected against self-injury and against external stimuli that would aggravate over-stimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given before performing gastric lavage.
Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required 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 and agents used for ADHD and nootropics, centrally acting sympathomimetics.

ATC code: N06BA04

Mechanism of action: This medicinal product 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. (Pharmacokinetic properties) and section 4.2 (Posology and method of administration).

The mechanism by which this medicinal product 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 containing *d*- and *I*-enantiomers, where the *d*-enantiomer is considered as the pharmacologically active enantiomer.

5.2 Pharmacokinetic properties

Absorption

This medicinal product 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 Pharmacodynamic properties). 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 this medicinal product is similar (bioequivalent) to the intact capsule. It 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 this medicinal product 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 content:

Microcrystalline cellulose spheres
Hypromellose
Ethylcellulose
Hydroxypropylcellulose
Dibutyl sebacate
Povidone
Talc

Capsule shell:

Hypromellose
Titanium dioxide (E171)
Iron oxide red (E172)

Printing ink:

Shellac
Black iron oxide (E172)
Propylene glycol
Ammonia solution
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE bottles with child-resistant PP twist-off caps containing a desiccant

Pack sizes: 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

Genus Pharmaceuticals Ltd.
(trading as ‘STADA’),
Linthwaite,
Huddersfield,
HD7 5QH,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0400

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2022

10 DATE OF REVISION OF THE TEXT

20/10/2025