SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Delmosart 27mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 27 mg of methylphenidate hydrochloride equivalent to 23.3 mg of methylphenidate.

Excipient with known effect: contains 184.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

27 mg Tablet: Capsule-shaped, biconvex, grey tablet, 6.7 mm x 12.0 mm, with “2393” printed on one side in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention-Deficit/Hyperactivity Disorder (ADHD)

Delmosart 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 an adult psychiatrist.

Special Diagnostic Considerations for ADHD in children

Diagnosis should be made according to the current DSM criteria or ICD guidelines and should be based on a complete history and evaluation of the patient. Third-party

corroboration is desirable and 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 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 the current DSM criteria or ICD guidelines, and should be based on a complete history and evaluation of the patient.

The specific etiology 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 instruments/interviews). Third-party corroboration is desirable and treatment 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 or 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 an adult psychiatrist.

Pre-treatment screening:

In adults new to Delmosart, and if required by national practice, cardiologist advice is needed prior to treatment initiation in order to check the absence of cardiovascular contraindications.

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

Ongoing monitoring:

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

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

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

- Weight should be recorded for 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 (illicit distribution), 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. A 27 mg dosage strength is available for those who wish to prescribe between the 18 mg and 36 mg dosages.

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

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

The maximum daily dosage of Delmosart is 54 mg in children.

The maximum daily dosage of Delmosart is 72 mg in adults.

Posology
Children

Children New to Methylphenidate: Delmosart may not be indicated in all children with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be considered sufficient to treat children new to methylphenidate. Careful dose titration by the physician in charge is required in order to avoid unnecessarily high doses of methylphenidate. The recommended starting dose of Delmosart for children who are not currently taking methylphenidate, or for children who are on stimulants other than methylphenidate, is 18 mg once daily.

Adults

Adults New to Methylphenidate: Delmosart may not be indicated in all adults with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be considered sufficient to treat adults new to methylphenidate. Careful dose titration by the physician in charge is required in order to avoid unnecessarily high doses of methylphenidate. The recommended starting dose of Delmosart for adults who are not currently taking methylphenidate, or for adults who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate: The recommended dose of Delmosart for patients who are currently taking methylphenidate three times daily at doses of 15 to 60 mg/day is provided in Table 1. Dosing recommendations are based on current dose regimen and clinical judgement.

TABLE 1

Recommended Dose Conversion from Other Methylphenidate Hydrochloride Regimens, where available, to Delmosart

Previous Methylphenidate Hydrochloride Daily Dose	Recommended Dose
5 mg Methylphenidate three times daily	18 mg once daily
10 mg Methylphenidate three times daily	36 mg once daily
15 mg Methylphenidate three times daily	54 mg once daily
20 mg Methylphenidate three times daily	72 mg once daily

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

Long-term (more than 12 months) use

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. In children and adolescents, 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 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 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.

Special populations
Elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group. Delmosart has not been studied in ADHD in patients older than 65 years.

Hepatic impairment

Methylphenidate has not been studied in patients with hepatic impairment.

Renal impairment

Methylphenidate has not been studied in patients with renal impairment.

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
Delmosart is for oral use once daily in the morning.

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

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

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 the risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis

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

4.4 Special warnings and precautions for use

Methylphenidate treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the patient's symptoms. When treatment of children is considered, assessment of the severity and chronicity of the child's symptoms should be related to the child's age (6-18 years).

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. Methylphenidate treatment should not and need not, be indefinite. In children and adolescents, 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) 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 the elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group. Delmosart has not been studied in ADHD in patients older than 65 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 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. Increases in diastolic and systolic blood pressure values were also observed in clinical trial data from adult ADHD patients. The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known. The possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data especially when treatment during childhood/adolescence is continued into adulthood. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which methylphenidate treatment 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. Methylphenidate should be discontinued in patients under treatment with repeated measures of tachycardia, arrhythmia or increased systolic blood pressure (>95th percentile) and referral to a cardiologist should be considered.

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 structural cardiac abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in patients, 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 patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

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. Before the start of treatment with methylphenidate, the patient should be examined for any existing psychiatric disorders and a family history with regard to psychiatric disorders should be obtained (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 (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. Aggression has been reported in patients treated with methylphenidate (see section 4.8). 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 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

Anxiety, agitation and tension have been reported in patients treated with methylphenidate (see section 4.8). Methylphenidate is also associated with the worsening of pre-existing anxiety, agitation or tension. Anxiety has led to discontinuation of methylphenidate in some patients. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.

Forms of bipolar disorder

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

Growth

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

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.

Use with serotonergic medicinal products

Serotonin syndrome has been reported following coadministration of methylphenidate with serotonergic medicinal products. If concomitant use of methylphenidate with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Methylphenidate must be discontinued as soon as possible if serotonin syndrome is suspected.

Abuse, misuse and diversion

Patients should be carefully monitored for the risk of diversion (illicit distribution), misuse and abuse of methylphenidate. Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

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

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

Withdrawal

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

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

Fatigue

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

Choice of methylphenidate formulation

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

Drug screening

This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test. Athletes must be aware that this medicinal product may cause a positive reaction to 'anti-doping' tests.

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 (see section 4.8).

Potential for gastrointestinal obstruction

Because the Delmosart tablet is nondeformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable prolonged-release formulations.

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.

Administration

Due to the prolonged-release design of the tablet, Delmosart should only be used in patients who are able to swallow the tablet whole. Patients should be informed that Delmosart must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed.

Excipient

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 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 effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

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

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

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

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

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

Use with alcohol
Alcohol may exacerbate the adverse CNS effect of psychoactive medicinal products, including methylphenidate. In-vitro data suggest that alcohol concentrations higher than 10% increase the cumulative release of MPH from Delmosart tablets. The clinical relevance of this finding on the MPH exposure after oral ingestion of Delmosart in combination with alcohol is not known. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with serotonergic medicinal products
There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic medicinal products. If concomitant use of methylphenidate with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important (see section 4.4). Methylphenidate must be discontinued as soon as possible if serotonin syndrome is suspected.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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 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 is excreted in human milk. Based on reports of breast milk sampling from five mothers, methylphenidate concentrations in human milk resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage, and a milk to maternal plasma ratio ranging between 1.1 and 2.7.

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

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

Fertility

No human data on the effect of methylphenidate on fertility are available. There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

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

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 or dental 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 reactions observed during clinical trials of children, adolescents, and adults and post-market spontaneous reports with Delmosart and those, which have been reported with other methylphenidate hydrochloride formulations. If the adverse reactions with Delmosart 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 (≥ 1/1,000 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	Adverse Reaction Frequency					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Nasopharyngitis, Upper respiratory tract infection[#], Sinusitis[#]				
Blood and lymphatic system disorders					Anaemia[†], Leucopenia[†], Thrombocytopenia, Thrombocytopenic purpura	Pancytopenia
Immune system disorders			Hypersensitivity reactions such as Angioneurotic oedema, Anaphylactic reactions, Auricular swelling, Bullous conditions,			

			Exfoliative conditions, Urticarias, Pruritus, Rashes, and Eruptions			
Metabolism and nutrition disorders*		Anorexia, Decreased appetite[†], Moderately reduced weight and height gain during prolonged use in children*				
Psychiatric disorders*	Insomnia, Nervousness	Affect lability, Aggression*, Agitation*, Anxiety*[†], Depression*[#], Irritability, Abnormal behaviour, Mood swings, Tics*, Initial insomnia[#], Depressed mood[#], Libido decreased[#], Tension[#], Bruxism**, Panic attack[#]	Psychotic disorders*, Auditory, visual and tactile hallucination*, Anger, Suicidal ideation*, Mood altered, Restlessness[†], Tearfulness, Worsening of pre-existing tics of Tourette's syndrome*, Logorrhoea, Hypervigilance, Sleep disorder	Mania*[†], Disorientation, Libido disorder, Confusional state[†], Obsessive-compulsive disorders and symptoms (including trichotillomania and dermatillomania, compulsive thoughts, compulsions)	Suicidal attempt (including completed suicide) * [†], Transient depressed mood*, Abnormal thinking, Apathy[†]	Delusions*[†], Thought disturbances*, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence, Paraesthesia[#], Tension headache[#]	Sedation, Tremor[†], Lethargy[#]		Convulsion, Choreoathetoid movements, Reversible ischaemic neurological deficit, Neuroleptic malignant syndrome (NMS; Reports were poorly documented and in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).	Cerebrovascular disorders*[†] (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion*, Migraine[†], Dysphemia
Eye disorders		Accommodation disorder[#]	Blurred vision[†], Dry eye[#]	Difficulties in visual accommodation, Visual impairment, Diplopia		Mydriasis, Increased intraocular pressure*, Glaucoma*
Ear and labyrinth disorders		Vertigo[#]				
Cardiac disorders*		Arrhythmia, Tachycardia, Palpitations	Chest pain	Angina pectoris	Cardiac arrest; Myocardial infarction	Supraventricular tachycardia, Bradycardia, Ventricular

						extrasystoles[†], Extrasystoles[†]
Vascular disorders*		Hypertension	Hot flush[#]		Cerebral arteritis and/or occlusion, Peripheral coldness[†], Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders		Cough, Oropharyngeal pain	Dyspnoea[†]			Epistaxis
Gastrointestinal disorders		Abdominal pain upper, Diarrhoea, Nausea[†], Abdominal discomfort, Vomiting, Dry mouth[†], Dyspepsia[#]	Constipation[†]			
Hepatobiliary disorders		Alanine aminotransferase increased[#]	Hepatic enzyme increased		Abnormal liver function, including acute hepatic failure and hepatic coma, Blood alkaline phosphatase increased, Blood bilirubin increased[†],	
Skin and subcutaneous tissue disorders		Alopecia, Pruritus, Rash, Urticaria, Hyperhidrosis[†]	Angioneurotic oedema, Bullous conditions, Exfoliative conditions	Macular rash, Erythema	Erythema multiforme, Exfoliative dermatitis, Fixed drug eruption	
Musculoskeletal and connective tissue disorders		Arthralgia, Muscle tightness[#], Muscle spasms[#]	Myalgia[†], Muscle twitching		Muscle cramps	Trismus**
Renal and urinary disorders			Haematuria, pollakiuria			Incontinence
Reproductive system and breast disorders		Erectile dysfunction[#]		Gynaecomastia		Priapism*, erection increased* and prolonged erection*
General disorders and administration site conditions		Pyrexia, Growth retardation during prolonged use in children*, Fatigue[†], Irritability[#], Feeling jittery[#], Asthenia[#], Thirst[#]	Chest pain		Sudden cardiac death*	Chest discomfort[†], Hyperpyrexia
Investigations		Changes in blood pressure and heart rate (usually an increase)*, Weight	Cardiac murmur*		Platelet count decreased, White blood cell count abnormal	

		decreased*				

* See section 4.4

** 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.

† Adverse drug reaction from clinical trials in adult patients that were reported with a higher frequency than in 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, and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdosage. Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. The efficacy of activated charcoal has not been established.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; centrally acting sympathomimetics: ATC code: N06BA04

Mechanism of action

Methylphenidate HCl is a mild central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Clinical efficacy and safety

Children
In the pivotal clinical studies, methylphenidate prolonged-release tablets were assessed in 321 paediatric patients already stabilised with immediate release preparations (IR) of methylphenidate and in 95 paediatric patients not previously treated with IR preparations of methylphenidate.

Clinical studies in paediatric patients showed that the effects of methylphenidate prolonged-release tablets were maintained until 12 hours after dosing when the product was taken once daily in the morning.

Adults
Short-term efficacy has been demonstrated for methylphenidate prolonged-release tablets in a dosage range of 18 to 72 mg/day. One thousand five hundred and twenty-three (1 523) adults with ADHD aged 18 to 65 years were evaluated in five double-blind, placebo-controlled studies of 5 to 13 weeks duration. methylphenidate prolonged-release tablets was evaluated in 2 fixed-dose studies and 3 flexible dose studies, using DSM-IV based instruments for the assessment of ADHD symptom severity in adults. In two fixed-dose studies, Conner's Adult ADHD Rating Scales (CAARS) showed that total scores of ADHD symptoms decreased, indicating an improvement in the severity of ADHD symptoms, from baseline to double-blind end point. In one fixed-dose study, all dose levels of methylphenidate prolonged-release tablets showed clinically significantly greater symptom control ($p<0.05$ for all dose levels), compared to placebo as measured by a reduction in CAARS total score. In the second fixed-dose study, methylphenidate prolonged-release tablets 72 mg/day but not methylphenidate prolonged-release tablets 54 mg/day proved to be statistically significant over placebo in reducing the CAARS ADHD symptoms total score from baseline to double-blind end point among adult subjects with ADHD (p-value 0.0024).

In two flexible dose studies, the LS mean changes from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS) total score at endpoint were statistically significant (Study 1: p=0.012; Study 2: p<0.001) for final methylphenidate prolonged-release tablets dose treatment over placebo (Study 1: -10.6 for methylphenidate prolonged-release tablets vs –6.8 for placebo; Study 2: -16.9 for methylphenidate prolonged-release tablets vs -12.0 for placebo). In the third flexible dose study (Study 3), methylphenidate prolonged-release tablets showed clinically significantly greater symptom control (p<0.0001) compared to placebo as measured by a reduction in CAARS total score. The LS mean change from baseline to Final Visit (Week 8) in the total ADHD Symptoms Scores of CAARS-O:SV was -10.9 in the methylphenidate prolonged-release tablets group and -6.9 in the placebo group (based on the ITT population).

In flexible dose Study 2, the magnitude of improvement in the total AISRS scores was statistically significantly larger in the methylphenidate prolonged-release tablets group than in the placebo group (p=0.0037). The LS mean (95% CI) difference from placebo was -5.3 (-8.9, -1.7). In flexible dose Study 3, the magnitude of improvement in the CAARS-O:SV scores was statistically significantly larger in the methylphenidate prolonged-release tablets group than in the placebo group (p=0.0063). The LS mean (95% CI) difference from placebo was -3.9 (-6.6, -1.1).

Adults treated with methylphenidate prolonged-release tablets in four long-term open-label studies over 6 to 12 months showed improvement in all efficacy endpoints evaluated, indicating stable effects over time on the reduction in ADHD symptoms. In one open-label study in a community setting, methylphenidate prolonged-release tablets treatment for up to 9 months showed improvement from baseline values in mean global assessment of efficacy scores by both the patient and the investigator. In a second study in which adults with ADHD received methylphenidate prolonged-release tablets for up to 1 year with a mean final dose of 67.4 mg/day showed clinically meaningful improvements from baseline in AISRS total scores with a mean change of -18.7 at the final visit. In a third long-term study of 48 weeks, adults with ADHD received methylphenidate prolonged-release tablets with a mean final dose of 46.6 mg/day showed a change from baseline in the mean DSM-IV Total ADHD symptoms score of CAARS by -17.2 at endpoint. In the fourth study, methylphenidate prolonged-release tablets was evaluated in a 52-week open label study in subjects who had previously completed a short-term placebo-controlled trial and short-term open-label extension. Adults with ADHD received methylphenidate prolonged-release tablets with a mean final dose of 53.8 mg/day showed stable effects over time on reductions in ADHD symptoms. Investigator-rated CAARS improved throughout the open-label phase, and was lower at endpoint (mean decrease by 1.9 from baseline).

5.2 Pharmacokinetic properties

Absorption

Methylphenidate is readily absorbed. Following oral administration of methylphenidate prolonged-release tablets in adults the tablet coating

dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The methylphenidate contained in the tablet core is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease. Methylphenidate prolonged-release tablets taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption of methylphenidate prolonged-release tablets once daily is generally comparable to conventional immediate release preparations.

Following the administration of methylphenidate prolonged-release tablets 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were: C_{max} 3.7 ± 1.0 (ng/mL), T_{max} 6.8 ± 1.8 (h), AUC_{inf} 41.8 ± 13.9 (ng.h/mL), and $t_{½}$ 3.5 ± 0.4 (h).

No differences in the pharmacokinetics of methylphenidate prolonged-release tablets were noted following single and repeated once daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of methylphenidate prolonged-release tablets 18 mg.
Following administration of methylphenidate prolonged-release tablets in single doses of 18 to 72 mg/day to adults, C_{max} and AUC_{inf} of methylphenidate were proportional to dose.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of methylphenidate prolonged-release tablets was approximately 3.5 h. The rate of protein binding of methylphenidate and of its metabolites is approximately 15%. The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Biotransformation

In humans, methylphenidate is metabolised primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPA, approximately 50 fold the level of the unchanged substance) which has little or no pharmacologic activity. In adults the metabolism of methylphenidate prolonged-release tablets once daily as evaluated by metabolism to PPA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of methylphenidate prolonged-release tablets is similar.

Elimination

The elimination half-life of methylphenidate in adults following administration of methylphenidate prolonged-release tablets was approximately 3.5 hours. After oral administration, about 90% of the dose is excreted in urine and 1 to 3% in faeces, as metabolites within 48 to 96 hours. Small quantities of

unchanged methylphenidate are recovered in urine (less than 1%). The main urinary metabolite is alpha-phenyl-piperidine acetic acid (60-90%).

After oral dosing of radiolabelled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

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

Special Populations

Gender
In healthy adults, the mean dose-adjusted AUC_{inf} values for methylphenidate prolonged-release tablets were 36.7 ng.h/mL in men and 37.1 ng.h/mL in women, with no differences noted between the two groups.

Race
In healthy adults receiving methylphenidate prolonged-release tablets, dose-adjusted AUC_{inf} was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age
The pharmacokinetics of methylphenidate prolonged-release tablets has not been studied in children younger than 6 years of age. In children 7-12 years of age, the pharmacokinetics of methylphenidate prolonged-release tablets after 18, 36 and 54 mg were (mean±SD): C_{max} 6.0 ± 1.3, 11.3 ± 2.6, and 15.0 ± 3.8 ng/mL, respectively, T_{max} 9.4 ± 0.02, 8.1 ± 1.1, 9.1 ± 2.5 h, respectively, and $AUC_{0\text{-}11.5}$ 50.4 ± 7.8, 87.7 ± 18.2, 121.5 ± 37.3 ng.h/mL, respectively.

Renal Insufficiency
There is no experience with the use of methylphenidate prolonged-release tablets in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolised and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of methylphenidate prolonged-release tablets.

Hepatic Insufficiency
There is no experience with the use of methylphenidate prolonged-release tablets in patients with hepatic insufficiency.

5.3 Preclinical safety data

Carcinogenicity

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development

Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content
Lactose monohydrate
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate
Fumaric acid
Methacrylic acid–methyl methacrylate copolymer
Triethyl citrate
Talc

Tablet coating
Polyvinyl alcohol, part hydrolyzed
Macrogol (3350)
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)
Iron oxide black (E172)

Printing ink
Shellac glaze
Iron oxide black (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf life after first opening the bottle: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

HDPE bottle with a child-resistant PP closure with silica gel desiccant integrated into the closure.

27 mg tablets: 28, 30 or 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1221

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/01/2025

10 DATE OF REVISION OF THE TEXT

13/10/2025