Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Delmosart PR 18 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 18 mg of methylphenidate hydrochloride equivalent to 15.6 mg of methylphenidate.

Excipient with known effect: contains 183.8 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

18 mg Tablet: Capsule-shaped, biconvex, yellow tablet, 6.6 mm x 11.9 mm, with "2392" printed on one side in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Attention-Deficit/HyperactivityDisorder(ADHD)
Delmosart PR 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.

Delmosart PR treatment is not indicated in all children with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing/diagnostic guidelines.

4.2 Posology and method of administration

Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

Pre-treatment screening:
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid

medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4).

Ongoing monitoring:
Growth, psychiatric and cardiovascular status should be continuously monitored (see 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 should be recorded at least 6 monthly with maintenance of a growth chart;
Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration
Careful dose titration is necessary at the start of treatment with Delmosart PR. Dose titration should be started at the lowest possible dose. A 27mg dosage strength is available for those who wish to prescribe between the 18 mg and 36 mg dosages.

For doses not realisable/practicable with this medicinal product, other strengths and medicinal products are available.

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

The maximum daily dosage of Delmosart PR is 54 mg.

PatientsNewto Methylphenidate: Clinical experience with Delmosart PR is limited in these patients (see section 5.1). Delmosart PR may not be indicated in all children with ADHD syndrome. Lower doses of short-acting methylphenidate formulations may be considered sufficient to treat patients 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 PR for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

PatientsCurrentlyUsing Methylphenidate: The recommended dose of Delmosart PR for patients who are currently taking methylphenidate three times daily at doses of 15 to 45 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 PR

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

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

Long-term (morethan12months)useinchildrenandadolescents

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 medicinal product for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy.

It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

Dose reductionanddiscontinuation
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
In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with Delmosart PR in adults is not appropriate (see sections 4.4 and 5.1).

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

Children under6 yearsof 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
Oral use
Delmosart PR must be swallowed whole with the aid of liquids, and must not be chewed, broken divided, or crushed (see section 4.4).
Delmosart PR may be administered with or without food (see section 5.2).
Delmosart PR is taken once daily in the morning.

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 isnotindicated in all children with ADHD and the decisionto usethemedicinal product mustbe based on avery thoroughassessment oftheseverity and chronicity of the child'ssymptomsinrelationtothechild's age.

Long-term use(morethan12months)inchildrenandadolescents
Thesafety andefficacyoflong-termuseofmethylphenidate has notbeensystematically evaluated incontrolledtrials. Methylphenidate treatment should not and neednot,beindefinite.Methylphenidate treatment is usually discontinued during orafter puberty.Patients on long-termtherapy (i.e.over 12 months)must havecarefulongoing monitoring according

totheguidancein sections4.2and4.4 for cardiovascular status, growth,appetite, developmentofde novo or worsening ofpre-existing psychiatricdisorders.Psychiatricdisordersto monitorforaredescribedbelow,and include (butarenotlimitedto) motororvocal tics,aggressiveorhostilebehaviour,agitation,anxiety,depression, psychosis,mania,delusions,irritability,lack ofspontaneity, withdrawalandexcessiveperseveration.

Thephysician whoelectsto use methylphenidate for extendedperiods (over12months) inchildren and adolescents with ADHD shouldperiodically re-evaluatethelong-termusefulnessofthe medicinalproductfortheindividualpatient withtrial periods off medication to assess the patient's functioningwithoutpharmacotherapy. Itis recommendedthat methylphenidate isde-challengedatleast onceyearly to assess the child'scondition (preferablyduringtimes of school holidays). Improvement maybe sustained when the medicinal product iseither temporarily or permanently discontinued.

Useinadults
Safety and efficacyhave not beenestablished for the initiationof treatment in adultsortheroutinecontinuation of treatment beyond 18 yearsofage.Iftreatmentwithdrawalhasnotbeen successfulwhen an adolescent has reached 18 yearsofagecontinuedtreatmentintoadulthood maybenecessary.The needforfurthertreatmentof these adults should be reviewedregularly andundertakenannually.

Useintheelderly
Methylphenidate should not beused in the elderly. Safety and efficacyhas not been establishedin thisagegroup.

Use inchildrenunder6yearsof age
Methylphenidate should not beused in children under the age of 6 years. Safety and efficacy in thisage grouphas not beenestablished.

Cardiovascularstatus
Patientswho are beingconsidered for treatmentwith stimulant medicationsshouldhave acarefulhistory (including assessmentfora family history of sudden cardiacor unexplaineddeath or malignant arrhythmia)andphysicalexam toassess for the presenceofcardiacdisease, and should receivefurtherspecialistcardiacevaluationif initial findings suggest such history ordisease. Patientswho develop symptomssuch as palpitations,exertionalchest pain, unexplainedsyncope, dyspnoea orother symptomssuggestiveof cardiacdisease during methylphenidate treatment should undergoa promptspecialist cardiac evaluation.

Analyses ofdata fromclinicaltrialsof methylphenidate inchildren and adolescentswith ADHDshowedthatpatients usingmethylphenidatemay commonly experiencechanges indiastolic and systolicbloodpressure ofover 10 mmHg relativeto controls.The short- and long-term clinicalconsequences of thesecardiovascular effects inchildren and adolescentsarenotknown. The possibility of clinical complicationscannotbe excludedasa result oftheeffects observedintheclinicaltrial dataespeciallywhen treatment during childhood/adolescenceis continued into adulthood. Caution isindicatedintreatingpatientswhoseunderlyingmedicalconditionsmight becompromisedby increasesinblood pressureorheartrate.Seesection4.3forconditionsinwhich methylphenidate treatment in contraindicated.

Cardiovascularstatusshouldbecarefullymonitored.Blood pressureandpulseshouldberecordedona centilechartateachadjustmentofdoseandthenatleastevery6months.

Theuseofmethylphenidate iscontraindicated in certain pre-existingcardiovasculardisordersunlessspecialist paediatric cardiac advicehasbeenobtained(seesection4.3).

Sudden death and pre-existingstructuralcardiacabnormalities orother serious cardiacdisorders

Suddendeath has beenreported in association withtheuseofstimulantsofthecentralnervoussystematusualdoses inchildren,some ofwhomhad structuralcardiac abnormalities orotherseriousheartproblems.Although some seriousheart problemsalonemay carryanincreased riskofsuddendeath,stimulant productsarenotrecommended inchildren or adolescentswith known structuralcardiac abnormalities,cardiomyopathy, serious heart rhythm abnormalities,or otherserious cardiac problems thatmayplacethematincreasedvulnerability to the sympathomimeticeffectsofastimulantmedicine.

Misuse andcardiovascular events
Misuse of stimulants of the central nervous systemmay be associated withsuddendeath andother serious cardiovascular adverseevents.

Cerebrovasculardisorders

Seesection4.3forcerebrovascular conditions in whichmethylphenidatetreatmentis contraindicated.Patients with additional risk factors(such as ahistoryofcardiovasculardisease, concomitantmedicationsthatelevateblood pressure) should beassessedatevery visitforneurological signsandsymptoms afterinitiating treatment with methylphenidate.

Cerebralvasculitisappears tobea veryrare idiosyncraticreaction tomethylphenidateexposure.There is little evidencetosuggestthat patients at higher risk canbe identified and the initial onsetofsymptomsmay bethe first indicationofanunderlyingclinicalproblem.Early diagnosis,based on ahighindexof suspicion, mayallow theprompt withdrawal of methylphenidate and earlytreatment.The diagnosis should thereforebe considered in any patientwho developsnew neurologicalsymptoms that are consistentwithcerebral ischemia during methylphenidatetherapy. These symptoms could include severe headache, numbness,weakness,paralysis,andimpairment of coordination, vision, speech,language or memory.

Treatmentwithmethylphenidateis notcontraindicatedinpatientswith hemiplegiccerebral palsy.

Psychiatric disorders

Co-morbidity of psychiatric disorders inADHDiscommon andshouldbe taken into accountwhen prescribing stimulant products.Inthecase ofemergentpsychiatricsymptoms orexacerbationof pre-existingpsychiatric disorders, methylphenidate should not begivenunlessthebenefitsoutweightherisks tothepatient.

Developmentorworseningofpsychiatricdisorders shouldbemonitored ateveryadjustmentofdose,thenat leastevery6 months,andateveryvisit;discontinuationoftreatmentmaybeappropriate.

Exacerbation ofpre-existing psychotic ormanicsymptoms

Inpsychoticpatients, administrationof methylphenidate mayexacerbatesymptoms ofbehavioural disturbanceand thoughtdisorder.

Emergenceof newpsychotic or manic symptoms

Treatment-emergentpsychotic symptoms (visual/tactile/auditoryhallucinationsand delusions) ormaniainchildren and adolescentswithout priorhistoryofpsychotic illness or mania can be caused bymethylphenidateatusual doses. Ifmanicorpsychotic symptomsoccur,consideration should be giventoa possiblecausalroleformethylphenidate, and discontinuationoftreatmentmaybeappropriate.

Aggressiveor hostile behaviour

Theemergenceorworseningofaggressionor hostilitycanbecausedbytreatmentwith stimulants.Patientstreated withmethylphenidate should be closely monitoredfortheemergenceorworseningof aggressivebehaviour or hostility attreatmentinitiation,atevery doseadjustmentand then at leastevery 6months and every visit.Physiciansshould evaluatetheneed for adjustmentof the treatment regimenin patientsexperiencingbehaviour changesbearing in mindthat upwardsor downwardstitration maybe appropriate. Treatment interruption canbe considered.

Suicidaltendency

Patientswith emergent suicidalideationorbehaviour during treatment for ADHD should be evaluated immediatelyby theirphysician.Considerationshouldbegiven to the exacerbationofan underlying psychiatriccondition and to a possiblecausalro le ofmethylphenidatetreatment.Treatmentofan underlying psychiatriccondition maybe necessary and consideration should be giventoa possiblediscontinuationofmethylphenidate.

Tics

Methylphenidate isassociatedwith the onset orexacerbation of motor and verbal tics.WorseningofTourette's syndrome has alsobeen reported.Family history should be assessedand clinical evaluation for tics or Tourette's syndrome inchildrenshould precedeuseofmethylphenidate.Patients should beregularlymonitoredforthe emergenceor worsening of tics during treatment withmethylphenidate.Monitoringshouldbeateveryadjustment ofdoseandthenatleastevery6monthsoreveryvisit.

Anxiety,agitation or tension

Methylphenidate isassociatedwith the worsening of pre-existinganxiety,agitationor tension.Clinical evaluation for anxiety, agitation ortension should precede use of methylphenidate and patients should beregularly monitoredfor theemergence orworseningofthesesymptomsduringtreatment,ateveryadjustmentofdoseandthenat leastevery6 months oreveryvisit.

Forms of bipolar disorder

Particular careshouldbe taken inusingmethylphenidate to treatADHD in patientswith comorbid bipolar disorder (including untreatedTypeIBipolar Disorderorother forms ofbipolardisorder)because ofconcern for possible precipitationofa mixed/manic episode in suchpatients. Priorto initiating treatment with methylphenidate,patients withcomorbiddepressivesymptoms shouldbeadequatelyscreenedto determine ifthey are at risk for bipolar disorder;such screening should include adetailed psychiatrichistory,includinga family history ofsuicide, bipolar disorder,and depression.Closeongoingmonitoringisessentialinthesepatients (seeabove'PsychiatricDisorders'andsection4.2).Patients shouldbemonitoredforsymptomsateveryadjustmentofdose,thenatleastevery6 months andateveryvisit.

Growth
Moderately reduced weight gain and growth retardationhave beenreported with the long-termuseof methylphenidate inchildren.

The effects of methylphenidate onfinal height and finalweightarecurrently unknown and beingstudied.

Growth shouldbemonitoredduringmethylphenidatetreatment:height, weight andappetiteshouldbe recordedatleast6 monthlywithmaintenanceofa growthchart.Patients whoarenotgrowing orgaining height or weight asexpectedmay need to havetheir treatment interrupted.

Seizures
Methylphenidate should beused withcautionin patients with epilepsy. Methylphenidate may lower the convulsive threshold inpatients with prior history ofseizures,in patientswith priorEEGabnormalities inabsence of seizures,and rarely inpatients withoutahistory ofconvulsions and no EEGabnormalities. If seizurefrequency increases or new- onsetseizures occur,methylphenidate should be discontinued.

Abuse,misuseanddiversion
Patientsshouldbe carefully monitored for the risk of diversion, misuse and abuse of methylphenidate. Methylphenidate should beused withcautionin patients with known drugor alcoholdependency because of a potentialforabuse,misuse ordiversion.

Chronicabuse of methylphenidate can lead to marked tolerance and psychological dependencewith varying degrees ofabnormalbehaviour.Frankpsychoticepisodes can occur, especially inresponseto parenteral abuse.

Patientage,thepresenceof risk factorsforsubstance usedisorder (suchasco-morbidoppositional-defiantor conductdisorder and bipolar disorder), previousorcurrentsubstanceabuse should all be takeninto account when decidingona course oftreatmentforADHD. Caution is called for inemotionally unstablepatients, suchasthose with ahistoryofdrug oralcoholdependence,becausesuch patientsmay increasethedosageontheir owninitiative.

For some high-risksubstanceabusepatients, methylphenidate orother stimulants may not besuitable and non- stimulant treatment should beconsidered.

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.

Withdrawal
Carefulsupervisionisrequired during methylphenidate withdrawal, sincethismay unmaskdepressionaswellas chronic over-activity.Somepatientsmay requirelong-termfollowup.

Careful supervisionis required during withdrawal fromabusive use since severe depression mayoccur.

Fatigue
Methylphenidate should not beused for the prevention or treatment ofnormal fatigue states.

Choiceofmethylphenidateformulation
Thechoiceof formulationofmethylphenidate-containing productwillhave tobedecided bythetreating specialist on an individualbasisanddepends on the intendedduration ofeffect.

Drugscreening

Thisproductcontains methylphenidate which mayinducea falsepositivelaboratorytest for amphetamines, particularlywith immunoassay screen test.

Renalorhepaticinsufficiency
There isnoexperiencewith the use of methylphenidateinpatients with renal orhepaticinsufficiency.

Haematologicaleffects
Thelong-termsafety of treatment with methylphenidate isnotfully known.In the eventofleukopenia, thrombocytopenia,anaemia or otheralterations,includingthose indicativeofserious renalorhepaticdisorders, discontinuationof treatment should be considered.

Administration
Dueto the prolonged-releasedesignof the tablet, Delmosart PRshouldonly be used in patientswhoareable to swallowthetabletwhole.Patients should beinformedthatDelmosart PRmust be swallowed whole withtheaidof liquids.Tabletsshouldnotbechewed, broken, divided,or crushed.

Excipient lactose
Thismedicinalproductcontains lactose. Patients withrarehereditaryproblemsofgalactose intolerance,theLapp lactase deficiency or glucose-galactose malabsorptionshouldnottakethis medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacokineticinteraction
It is not known how methylphenidate may effect plasma concentrations of concomitantly administered medicinal products. Therefore, caution is recommended at combining methylphenidate with other medicinal products, especially those with a narrow therapeutic window.

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

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, 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 medicines already being taken and establish plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamicinteractions
Anti-hypertensive medicines
Methylphenidate may decrease the effectiveness of medicinal products used to treat hypertension.

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

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

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

Usewith 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)
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 medicines
Caution is recommended when administering methylphenidate with dopaminergic medicinal products, including antipsychotics. Because a predominant action of methylphenidate is to increase extracelluar 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 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.

Fertility
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.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials of children, adolescents, and adults and post-market spontaneous reports with Delmosart PR and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with Delmosart PR 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	Frequency					

Class						
	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	Anorexia, Affect lability, Aggression*, Agitation*, Anxiety*[†], Depression*, Irritability, Abnormal behaviour, Mood swings, Tics*, Initial insomnia[#], Depressed mood[#], Depression[#], Libido decreased[#], Tension[#],	Psychotic disorders*, Auditory, visual and tactile hallucination*, Anger, Suicidal ideation*, Mood altered, Restlessness[†], Tearfulness, Worsening	Mania*[†], Disorientation, Libido disorder, Confusional state[†]	Suicidal attempt (including completed suicide) * [†], Transient depressed mood*, Abnormal thinking, Apathy[†], Repetitive behaviours, Over-focussing	Delusions*[†], Thought disturbances*, dependence. Cases of abuse and dependence have been described, more often with immediate release formulations

		Bruxism[#], Panic attack[#]	of pre-existing tics of Tourette's syndrome *, Logorrhoea, Hypervigilance, Sleep disorder			
Nervous system disorders	Headache	Dizziness, Dyskinesia, Psychomotor hyperactivity, Somnolence, Paresthaesia[#], 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 medicinal products, so the role of methylphenidate is unclear).	Cerebrovascular disorders*[†] (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion*, Migraine[†]
Eye disorders		Accommodation disorder[#]	Blurred vision[†], Dry eye[#]	Difficulties in visual accom-modation, Visual impairment, Diplopia		Mydriasis
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[†]			
Gastrointestinal disorders		Abdominal pain upper, Diarrhoea,	Constipation[†]			

		Nausea†, Abdominal discomfort, Vomiting, Dry mouth†, Dyspepsia#				
Hepatobiliary disorders			Hepatic enzyme elevations		Abnormal liver function, including hepatic coma	
Skin and subcutaneous tissue disorders		Alopecia, Pruritis, Rash, Urticaria	Angioneurotic oedema, Bullous conditions, Exfoliative conditions	Hyperhidrosis†, 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 decreased*, Alanine aminotransferase increased#	Cardiac murmur*, Hepatic enzyme increased		Blood alkaline phosphatase increased, Blood bilirubin increased†, Platelet count decreased, White blood cell count abnormal	

* See section 4.4

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

† Frequency derived from clinical trials in children and adolescent and reported at a higher frequency in clinical trials in adult patients.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: + 353 1 6762517. Website: www.hpra.ie, Email: medsafety@hpra.ie.

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

Mechanismof 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.

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

Clinical studies 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.

Eight hundred ninety-nine (899) adults with ADHD aged 18 to 65 years were evaluated in three double-blind, placebo-controlled studies of 5 to 13 weeks duration. Some short-term efficacy has been demonstrated for methylphenidate prolonged-release tablets in a dosage range of 18 to 72 mg/day, but this has not been consistently shown beyond 5 weeks. In one study, in which response was defined as at least a 30% reduction from baseline in Conners' Adult ADHD Rating Scales (CAARS) ADHD Symptoms total score at Week 5 (endpoint) and analysed assuming subjects with missing data at their final visit were non-responders, a significantly higher proportion of patients responded to treatment with methylphenidate prolonged-release tablets at doses of 18, 36, or 72 mg/day compared to placebo. In the two other studies, when analysed assuming subjects with missing data at their final visit were non-responders, there were numerical advantages for methylphenidate prolonged-release tablets compared to placebo but a statistically significant difference in the proportion of patients meeting predefined response criteria was not demonstrated between methylphenidate prolonged-release tablets and placebo.

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 methylphenidate 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 methylphenidate 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, 36, and 54 mg/day to adults, C_{max} and $AUC_{(0\text{-}inf)}$ 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.

SpecialPopulations
Gender
In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ 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 $AUC_{(0\text{-}inf)}$ 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.

HepaticInsufficiency
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/foetaldevelopment
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

Carcinogenicity
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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
18 mg prolonged-release tablets:
Polyvinyl alcohol, part hydrolyzed
Macrogol (3350)
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

Shelf life after first opening the bottle:
18 mg tablets: 3 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.

18 mg tablets: 28, 30 or 90 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/147/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th September 2016

10 DATE OF REVISION OF THE TEXT

December 2019