SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tuzulby 40 mg prolonged-release chewable tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tuzulby 40 mg prolonged-release chewable tablets
Each tablet contains 40 mg methylphenidate hydrochloride equivalent to 34.59 mg of methylphenidate.

Excipient with known effect

Each tablet contains 12.2 mg aspartame (E 951).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release chewable tablet.

Tuzulby 40 mg prolonged-release chewable tablets are speckled, off white, 8.5 x 18.5 mm capsule shaped coated tablet, debossed with “NP14” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tuzulby is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children and adolescents 6-17 years old 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 Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria or the guidelines in International Classification of Diseases, Tenth Revision (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 symptoms.

4.2 Posology and method of administration

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

Posology

Tuzulby prolonged-release chewable tablets consists of an immediate release component (30% of the dose, which ensures rapid onset of action) and a prolonged-release component (70% of the dose, which is designed to maintain therapeutic plasma levels over an extended period). This medicinal product is designed to deliver therapeutic plasma levels for a period of approximately 8 hours following administration (see also section 5.2).

Dose titration
Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

Other methylphenidate-containing medicinal products with different strengths may be available.
Switching from immediate-release methylphenidate-containing medicinal products to Tuzulby prolonged-release chewable tablets, administered as a single dose, provides comparable overall exposure of methylphenidate compared to the same total dose of the immediate release formulation administered twice daily.
The recommended dose of Tuzulby should be equal to the total daily dose of the immediate-release methylphenidate-containing formulation not exceeding a total dose of 60 mg. Examples are provided in the table below.

Immediate-release methylphenidate dose	**Tuzulby dose**
10 mg methylphenidate twice daily	20 mg once daily
15 mg methylphenidate twice daily	30 mg once daily
20 mg methylphenidate twice daily	40 mg once daily
30 mg methylphenidate twice daily	60 mg once daily

Treatment of hyperkinetic disorders/ADHD in children and adolescents (from 6 years to less than 18 years of age)
For patients from 6 years to less than 18 years of age, the recommended starting dose is 20 mg given orally once daily in the morning. The dose may be titrated up or down weekly in increments of 10 mg, 15 mg or 20 mg. The 10 mg and 15 mg doses can each be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively. The dose should be individualised according to the treatment needs and responses of the patient.

The maximum daily dose of methylphenidate is 60 mg for treatment of children and adolescents (from 6 years to less than 18 years of age) with ADHD.

Long term (more than 12 months) use in children and adolescents (from 6 years to less than 18 years of age)
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 (more than 12 months) in children and adolescents (from 6 years to less than 18 years of age) 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 school holidays). Improvement may be sustained when the medicinal product is either temporarily or permanently discontinued.

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

Special populations

Adults
Methylphenidate is not indicated for use in adults in ADHD. Safety and efficacy have not been established in this age group.

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

Hepatic impairment
Methylphenidate has not been studied in patients with hepatic impairment. Caution should be exercised in these patients.

Renal impairment
Methylphenidate has not been studied in patients with renal impairment. Caution should be exercised in these patients.

Paediatric population

Methylphenidate should not be used in children under the age of 6 years. The safety and efficacy of methylphenidate in this age group have not been established.

Method of administration

Tuzulby is for oral use.

Tuzulby should be administered orally once daily in the morning with or without food (see section 5.2).

Tuzulby must be chewed and not swallowed whole or crushed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Glaucoma

- Phaechromocytoma
- During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicinal products, due to risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
- Diagnosis or history of severe and episodic (Type 1) 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) (see section 4.4)
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders

4.4 Special warnings and precautions for use

The decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the child's/adolescent's symptoms in relation to the child's/adolescent's age.

Pre-treatment screening
Prior to prescribing, it is necessary to conduct a baseline evaluation of the patient's cardiovascular status, including blood pressure and heart rate. A comprehensive medical history should document concomitant medicinal products, past and present comorbid medical and psychiatric disorders or symptoms, family history of sudden cardiac or unexplained death or malignant arrhythmia, and accurate recording of pre-treatment height and weight on a growth chart (see section 4.3).

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

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the 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/adolescent's condition (preferably during times of school holidays). Improvement may be sustained when the medicinal product is either temporary or permanently discontinued.

Cardiovascular status

Patients who are being considered for treatment with stimulant medicinal products should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical examination to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms, such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long- term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See section 4.3 for conditions in which methylphenidate treatment is contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on centile chart at each adjustment of dose and then at least every 6 months.

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system (CNS) at usual doses in children and adolescents, 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 medicinal products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicinal product.

Misuse and cardiovascular events

Misuse of stimulants of the CNS may be associated with sudden death and other serious cardiovascular adverse reactions.

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

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

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

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

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

Emergence of new psychotic or manic symptoms
Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses (see section 4.8). If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate and discontinuation of treatment may be appropriate.

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

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

Tics
Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension
Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.

Bipolar disorder
Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close ongoing monitoring is essential in these patients (see above 'Psychiatric Disorders' and section 4.2). Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.

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

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

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

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.

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.

Abuse, misuse and diversion

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

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse, or diversion.

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

Patient’s age, the presence of risk factors for substance use disorder (such as comorbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should 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 withdrawal, since this may unmask depression as well as chronic overactivity. Some patients may require long term follow-up.

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

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.

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 leucopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Priapism
Prolonged and painful erections have been reported in association with methylphenidate products, mainly in association with a change in the methylphenidate treatment regimen. Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Excipients with known effect

Aspartame (E 951)
Tuzulby 20 mg prolonged-release chewable tablets contains 6.1 mg of aspartame (E 951) in each tablet.
Tuzulby 30 mg prolonged-release chewable tablets contains 9.15 mg of aspartame (E 951) in each tablet.
Tuzulby 40 mg prolonged-release chewable tablets contains 12.2 mg of aspartame (E 951) in each tablet.
Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria, a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release chewable tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

It is not known how methylphenidate may affect plasma concentrations of concomitantly administered medicinal products. Therefore, caution is recommended at combining methylphenidate with other medicinal products, especially those with 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, primodone), and some antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors). When starting and stopping treatment with methylphenidate, it may be necessary to adjust the dose of these medicinal products already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

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

Use with medicinal products that elevate blood pressure
Caution is advised in patients being treated with methylphenidate with other medicinal products 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 two weeks) with MAO inhibitors (see section 4.3).

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

Use with halogenated anaesthetics
There is a risk of sudden blood pressure 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 α_2-agonists (e.g., clonidine)
Serious adverse reactions, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic medicinal products
Caution is recommended when administering methylphenidate with dopaminergic medicinal products, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and

indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

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 1 000 women who received 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 reports.

Animal studies have shown reproductive toxicity at maternally toxic doses (see section 5.3).

Methylphenidate should not be used during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Breast-feeding

Methylphenidate has been detected in breast milk of women 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 newborn/infants 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.
Methylphenidate did not impair fertility in male or female mice.
No clinically relevant effects on fertility were observed in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In general, the most common adverse reactions associated with methylphenidate treatment have been reported with a very common frequency are decreased appetite, insomnia, nervousness, headache, nausea and dry mouth.

Tabulated list of adverse reactions

Table 1 below shows all adverse reactions reported during clinical trials and post-marketing experience with methylphenidate, as well as those adverse reactions which have been reported with other methylphenidate hydrochloride formulations. If adverse reactions frequencies reported with methylphenidate and other methylphenidate hydrochloride formulations were different, the highest frequency from the safety databases was used.

Adverse reactions are listed by MedDRA system organ class and frequency convention as follows: 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 available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Adverse reactions	Frequency category
Infections and infestations	Nasopharyngitis	Common
Blood and lymphatic system disorders	Leucopenia, thrombocytopenia anaemia, thrombocytopenic purpura	Very rare
	Pancytopenia	Not known
Immune system disorders	Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus*, rashes and eruptions*	Uncommon
Metabolism and nutrition disorders*	Decreased appetite**	Very common
	Anorexia, moderately reduced weight, height gain decelerated*	Common
Psychiatric disorders*	Insomnia, nervousness	Very common
	Abnormal behaviour, aggression*, affect lability, agitation*, anorexia, anxiety*, depression*, irritability, restlessness** sleep disorder**,	Common

	libido decreased**, panic attack, stress, bruxism	
	Hypervigilance, auditory, visual, and tactile hallucinations*, mood altered, mood swings, anger, suicidal ideation*, tearfulness, psychotic disorders*, tics*, worsening of pre-existing tics or Tourette's syndrome*, tension, emotional poverty	Uncommon
	Mania*, disorientation, libido disorder , obsessive-compulsive disorder (including trichotillomania and dermatillomania)	Rare
	Suicidal attempt, suicide*, transient depressed mood*, abnormal thinking, apathy	Very rare
	Delusions*, thought disturbances*, confusional state, dependence, logorrhoea*****	Not known
Nervous system disorders	Headache	Very common
	Tremour**, somnolence, dizziness, dyskinesia, psychomotor hyperactivity	Common
	Sedation, akathisia, decreased apetite	Uncommon
	Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS) ***	Very rare
	Cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine, dysphemia	Not known
Eye disorders	Diplopia, blurred vision , dry eye******	Uncommon
	Difficulties in visual accommodation, mydriasis, visual disturbance	Rare
	Increased intraocular pressure, Glaucoma	Not known
Cardiac disorders	Tachycardia, palpitations, arrhythmia	Common

	Chest pain	Uncommon
	Angina pectoris	Rare
	Cardiac arrest, myocardial infarction	Very rare
	Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles	Not known
Vascular disorders	Hypertension, peripheral coldness**	Common
	Cerebral arteritis and/or occlusion, Raynaud's phenomenon	Very rare
Gastrointestinal disorders	Nausea**, dry mouth**	Very common
	Abdominal pain, diarrhoea, stomach discomfort, vomiting, dyspepsia*, toothache*	Common
	Constipation	Uncommon
Hepatobiliary disorders	Hepatic enzyme elevations	Uncommon
	Abnormal liver functions, including hepatic coma	Very rare
Skin and subcutaneous tissue disorders	Hyperhidrosis**, alopecia, pruritus, rash, urticaria	Common
	Angioneurotic oedema, bullous conditions, exfoliate conditions	Uncommon
	Macular rash, erythema	Rare
	Erythema multiforme, exfoliate dermatitis, fixed drug eruption	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Myalgia, muscle twitching, muscle tightness	Uncommon
	Muscle spasms	Very rare
	Trismus	Not known
Renal and urinary disorders	Haematuria	Uncommon
	Incontinence	Not known
Reproductive system and breast disorders	Gynaecomastia	Rare
	Erectile dysfunction, priapism, erection increased and prolonged erection	Not known
General disorders and administration site conditions	Pyrexia, growth retardation during prolonged use in children and adolescents*, feeling jittery, fatigue**, thirst	Common
	Chest pain	Uncommon
	Sudden cardiac death*	Very rare
	Chest discomfort, hyperpyrexia	Not known
Investigations	Changes in blood pressure and	Common

	heart rate (usually an increase)[*], weight decreased[*]	
	Cardiac murmur[*], hepatic enzyme increased	Uncommon
	Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal	Very rare

* See section 4.4 "Special warnings and precautions for use"

** Adverse reactions from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents.

*** Reports were poorly documented and in most cases, patients were also receiving other medicinal products, so the role of methylphenidate is unclear

**** These usually occur at the beginning of treatment and may be alleviated by concomitant food intake

***** Cases of abuse and dependence have been described, more often with immediate release formulations.

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

Description of selected adverse reactions

Very rare cases of sudden death have been also reported in association with the use of stimulants of the CNS at usual doses in children, some of whom had structural cardiac abnormalities or other serious heart problems. Cardiovascular status should be carefully assessed and monitored (see section 4.4.).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play 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 system, may result in vomiting, agitation, tremours, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

Treatment

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

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures for gastrointestinal detoxification include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given before performing gastric lavage.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, psychostimulants, agents use for ADHD and nootropics, ATC code: N06BA04

Mechanism of action

Methylphenidate is a CNS stimulant (psychostimulant) with more pronounced effects on central than on motor activities. Methylphenidate exists in four stereoisomers, with the threo-form being the pharmacodynamically active configuration. The D-isomer is pharmacologically more active than the L-isomer.

The mechanism of action in humans is not fully understood; however, it is thought that the effect is due to inhibition of dopamine reuptake in the striatum without triggering a release of dopamine. In particular, methylphenidate binds to dopamine transporters (DAT) and norepinephrine transporters (NET) that are usually responsible for the reuptake of these neurotransmitters from the synaptic cleft. It blocks these transporters causing an increase in synaptic levels of dopamine (DA) and norepinephrine (NE) and an increase in extracellular DA in the striatum, nucleus accumbens, and prefrontal cortex. Both the DA receptor subtypes 1 (D1) and 2 (D2), as well as the μ-opioid receptor are important for the rewarding and therapeutic effects of MPH. Nevertheless, the mechanism by which methylphenidate produces the cognitive and behavioural effects has not been clearly established.

The central stimulating effect is expressed, among other things, in an increase in the ability to concentrate, readiness to perform and make decisions, psychophysical activity as well as in suppression of tiredness and physical fatigue. The indirect sympathomimetic effect of methylphenidate in humans can also lead to an increase in blood pressure, acceleration of the pulse rate and a reduction in the tone of the bronchial muscles. These effects are usually not very pronounced. Methylphenidate

can reduce appetite and, at high doses, lead to an increase in body temperature. Behavioural stereotypies can also be triggered at high doses or after prolonged use.

Population pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation

Population PK models were developed for methylphenidate for extended- and the immediate-release formulations. Similarity across extended-release treatment with respect to the PD outcome was shown.
Modelling and simulation assessed the impact of differences in PK profile shape between extended- and the immediate-release formulations on efficacy, represented as SKAMP score in the target population of children with ADHD. The results of the analysis supported the claimed clinical noninferiority in the 12 hours post dose time frame for the proposed extended-release formulations compared to the immediate-release formulation.

Clinical efficacy and safety studies

The efficacy of Methylphenidate hydrochloride was evaluated in a multicenter, dose-optimised, double-blind, randomised, placebo-controlled study conducted in 90 paediatric subjects in a laboratory classroom. Eligible subjects were males or females, aged 6 through 12 years, with a diagnosis of combined or inattentive ADHD and need for pharmacological treatment for their condition. Diagnosis was performed using the Schedule for Affective Disorders and Schizophrenia (K-SADS), Clinical Global Impression of Severity (CGI-S; score ≥ 3), and Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS; ≥ 90^{th} percentile in hyperactive-impulsive subscale, inattentive subscale, or total score). The study began with a 6-week open-label dose optimization period with an initial Methylphenidate hydrochloride dose of 20 mg. Patients were instructed to chew each tablet once daily in the morning. The dose could be titrated weekly in increments of 10 to 20 mg until an optimal dose or the maximum dose of 60 mg/day was reached. Eighty-six (86) of the 90 enrolled subjects then entered a 1-week randomized, double-blind, parallel group treatment period with the individually optimized dose of Methylphenidate hydrochloride or placebo. At the end of the double-blind treatment period, the laboratory classroom raters and teachers evaluated the attention and behavior of the subjects, throughout the day using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The SKAMP-Combined score, measured at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose during the laboratory classroom day at the end of the double-blind treatment period, was used to assess the primary and the key secondary efficacy parameters. The primary efficacy endpoint was the average of treatment effects across all the time points as specified above during the classroom day. The key secondary efficacy parameters were onset and duration of clinical effect.
In total 85 subjects were evaluated, with a mean (standard deviation, SD) age of 9.6 (1.69) years, both male and female subjects, of either Hispanic/Latino or non-Hispanic/Latino ethnicity, 27.1% having inattentive ADHD type and 72.9 % with combine ADHD type, all of whom having an ADHD-RS at ≥ 90^{th} percentile at baseline. Overall, 39 (43.3%) subjects had taken prior medications. The most common prior medications were centrally acting sympathomimetics (37.8%). Methylphenidate hydrochloride was statistically significantly superior to placebo with respect to the primary endpoint. Methylphenidate hydrochloride also showed improvement over placebo at 0.75, 2, 4, and 8 hours post-dosing. The onset of efficacy for Methylphenidate hydrochloride was determined to be 2 hours post-dose, and efficacy was maintained through the 8-hour time point. SKAMP subscale scores paralleled the SKAMP-Combined score. The main results of the primary and key secondary efficacy variables obtained from the study are presented in the below table (Table 2).

Table 2. Results of the primary and key secondary efficacy variables

Efficacy endpoints	Placebo	Methylphenidate hydrochloride	Treatment difference
Primary endpoint: **Post-dose SKAMP-Combined scores at visit 9**			
Average overall post-dose time-points			
n	43	42	
LS mean (SE)	19.1 (1.39)	12.1 (1.41)	-7.0 (1.99), p < 0.001
Key secondary endpoints: **Post-dose SKAMP-Combined scores at visit 9**			
0.75 hour post-dose	18.3 (1.60)	10.2 (1.62)	-8.2 (2.28), p < 0.001
2 hour post-dose	20.3 (1.60)	7.5 (1.62)	-12.8 (2.28), p < 0.001
4 hour post-dose	19.9 (1.60)	7.6 (1.62)	-12.3 (2.28), p < 0.001
8 hour post-dose	19.4 (1.60)	11.6 (1.62)	-7.8 (2.28), p < 0.001
10 hour post-dose	17.7 (1.60)	14.3 (1.62)	-3.4 (2.28), p = 0.133
12 hour post-dose	19.4 (1.60)	16.5 (1.62)	-2.9 (2.28), p = 0.206
13 hour post-dose	18.5 (1.60)	16.9 (1.62)	-1.6 (2.28), p = 0.496
Post-dose PERMP scores at visit 9			
Average over all post-dose time points			
n	43	42	
LS mean (SE)	103.5 (7.20)	128.0 (7.30)	24.5 (10.25), p = 0.017

LS: least squares; PERMP: Permanent Product Measure of Performance; SE: standard error; SKAMP: Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale.
Both Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) scores improved during the open-label dose optimisation period. At the end of the open-label phase, all subjects were considered either much improved or very much improved on the CGI-I. Improvements were also observed on the ADHD- Rating Scale (RS) during the open-label dose optimisation period, and most subjects were considered ADHD-RS responders. All Comprehensive Psychopathological Rating Scales (CPRS) showed a decrease in scores between baseline and visit 8.

5.2 Pharmacokinetic properties

Absorption

The active substance methylphenidate hydrochloride is rapidly and almost completely absorbed from the immediate-release tablets. Owing to extensive first-pass metabolism the absolute bioavailability was 22±8% for the d-enantiomer and 5±3% for the l-enantiomer. Peak plasma concentrations (C_{max}) of approximately 11 ng/ml are attained, on average, 1-2 hours after administration of 0.30 mg/kg. The area under the concentration-time curve (AUC) and the C_{max}, are proportional to the dose.

Following a single oral dose of 40 mg Methylphenidate hydrochloride under fasting conditions, plasma methylphenidate reached maximal concentration (C_{max}) at a median time of 5 hours after dosing. Methylphenidate C_{max} and exposure (area under the curve, AUC) were approximately 12 ng/ml and 112 ng×h/ml, respectively.

Following a single oral dose of 40 mg under fed conditions, Methylphenidate hydrochloride exhibited C_{max} and AUC values of approximately 15 ng/ml and 133 ng×h/ml, respectively. Both AUC and C_{max} were also proportional to dose between the dose range of 20-40 mg after a single dose of Tuzulby in healthy subjects under fed conditions.

There is considerable inter- and intra-individual variation in plasma concentration.

Food effect
High-fat meal had no effect on the time to peak concentration, and increased C_{max} and systemic exposure ($AUC_{0-\infty}$) of methylphenidate by about 20% and 4%, respectively, after a single dose administration of 40 mg Methylphenidate hydrochloride .

Distribution

In the blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Binding of methylphenidate and its metabolites to plasma proteins is low at 10-33%. The volume of distribution is 2.65±1.11 L/kg for d-methylphenidate and 1.80±0.91 L/kg for l- methylphenidate.

Biotransformation

Methylphenidate is rapidly and almost completely metabolised by the carboxylesterase CES1A1. It is primarily broken down into ritalinic acid. Peak plasma levels of ritalinic acid are reached approximately 2 hours after dosing with an immediate release formulation and are 30 to 50 times higher than those of methylphenidate. The half-life of ritalinic acid is approximately twice that of methylphenidate and the systemic clearance is 0.17 l/h/kg. This allows accumulation in patients with renal insufficiency. Since ritalinic acid has little or no pharmacodynamic activity, this plays a minor role therapeutically. Only small amounts of hydroxylated metabolites (e.g., hydroxymethylphenidate and hydroxyritalinic acid) are detectable.
Therapeutic activity seems to be mainly limited to methylphenidate.

Elimination

Plasma methylphenidate concentrations decline monophasically following oral administration of Methylphenidate hydrochloride . The mean plasma terminal elimination half-life of methylphenidate was about 5. hours in healthy volunteers following a single 40 mg dose administration. Only small amounts (< 1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60-86%), presumably independent of pH.

There appear to be no differences in the pharmacokinetics of methylphenidate between children with hyperkinetic disorders/ADHD and healthy adult subjects. Elimination data from patients with normal renal function suggest that renal elimination of unmetabolised methylphenidate is hardly affected by impaired renal function. Renal excretion of the main metabolite ritalinic acid may be reduced.

5.3 Preclinical safety data

Carcinogenicity

In lifetime 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-embryonic/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

Sodium polystyrene sulfonate
Povidone (E 1201)
Triacetin (E 1518)
Polyvinyl acetate
Sodium lauryl sulfate
Mannitol (E 421)
Xanthan gum (E 415)
Crospovidone (E 1202)
Microcrystalline cellulose (E 460)
Guar Gum (E 412)
Aspartame (E 951)
Citric Acid
Cherry Flavour
Talc (E 553b)
Silica colloidal hydrated
Magnesium stearate
Polyvinyl alcohol
Macrogol
Polysorbate 80 (E 433)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Pack size: 30 prolonged-release chewable tablets in a 60 mL HDPE bottle including a 2 g desiccant canister with a child-resistant cap (PP).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

30/10/2025