ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tuzulby 20 mg prolonged-release chewable tablets
Tuzulby 30 mg prolonged-release chewable tablets
Tuzulby 40 mg prolonged-release chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tuzulby 20 mg prolonged-release chewable tablets

Each tablet contains 20 mg methylphenidate hydrochloride equivalent to 17.30 mg of methylphenidate.

Excipient with known effect
Each tablet contains 6.1 mg aspartame (E 951).

Tuzulby 30 mg prolonged-release chewable tablets

Each tablet contains 30 mg methylphenidate hydrochloride equivalent to 25.95 mg of methylphenidate.

Excipient with known effect
Each tablet contains 9.15 mg aspartame (E 951).

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 20 mg prolonged-release chewable tablets are speckled, off white, 6.8 x 14.7 mm capsule shaped coated tablet, debossed with “N2” “N2” on one side and bisect on the other side.
The chewable tablet can be divided into equal doses.

Tuzulby 30 mg prolonged-release chewable tablets are speckled, off white, 7.7 x 16.8 mm capsule shaped coated tablet, debossed with “N3” “N3” on one side and bisect on the other side.
The chewable tablet can be divided into equal doses.

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

Tuzulbi 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.

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**, libido decreased**, panic attack, stress, bruxism	Common
	Hypervigilance, auditory, visual, and tactile hallucinations*, mood altered, mood swings, anger,	Uncommon

	suicidal ideation*, tearfulness, psychotic disorders*, tics*, worsening of pre-existing tics or Tourette's syndrome*, tension, emotional poverty	
	Mania*, disorientation, libido disorder	Rare
	Suicidal attempt, suicide*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focusing	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	Uncommon
	Difficulties in visual accommodation, mydriasis, visual disturbance	Rare
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 heart rate (usually an increase)[*], weight decreased[*]	Common
	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.

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 national reporting system listed in Appendix V.

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 LS mean (SE)	 43 19.1 (1.39)	 42 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 2 hour post-dose 4 hour post-dose 8 hour post-dose 10 hour post-dose 12 hour post-dose 13 hour post-dose	 18.3 (1.60) 20.3 (1.60) 19.9 (1.60) 19.4 (1.60) 17.7 (1.60) 19.4 (1.60) 18.5 (1.60)	 10.2 (1.62) 7.5 (1.62) 7.6 (1.62) 11.6 (1.62) 14.3 (1.62) 16.5 (1.62) 16.9 (1.62)	 -8.2 (2.28), p < 0.001 -12.8 (2.28), p < 0.001 -12.3 (2.28), p < 0.001 -7.8 (2.28), p < 0.001 -3.4 (2.28), p = 0.133 -2.9 (2.28), p = 0.206 -1.6 (2.28), p = 0.496
Post-dose PERMP scores at visit 9 Average over all post-dose time points n LS mean (SE)	 43 103.5 (7.20)	 42 128.0 (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 prolonged-release chewable tablets 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1907/001 (20 mg x 30 prolonged-release chewable tablets)
EU/1/24/1907/002 (30 mg x 30 prolonged-release chewable tablets)
EU/1/24/1907/003 (40 mg x 30 prolonged-release chewable tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

Neuraxpharm Arzneimittel GmbH
Elisabeth-Selbert-Straße 23
40764 Langenfeld
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON / BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Tuzulby 20 mg prolonged-release chewable tablets
methylphenidate hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release chewable tablet contains 20 mg methylphenidate hydrochloride

3. LIST OF EXCIPIENTS

Contains aspartame (E 951). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

prolonged-release chewable tablets

30 prolonged-release chewable tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1907/001 (20 mg x 30 prolonged-release chewable tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tuzulby 20 mg *(only for the outer carton)*

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON / BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Tuzulby 30 mg prolonged-release chewable tablets
methylphenidate hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release chewable tablet contains 30 mg methylphenidate hydrochloride

3. LIST OF EXCIPIENTS

Contains aspartame (E 951). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

prolonged-release chewable tablets

30 prolonged-release chewable tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1907/002 (30 mg x 30 prolonged-release chewable tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tuzulby 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. *(*

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON / BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Tuzulby 40 mg prolonged-release chewable tablets
methylphenidate hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release chewable tablet contains 40 mg methylphenidate hydrochloride

3. LIST OF EXCIPIENTS

Contains aspartame (E 951). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

prolonged-release chewable tablets

30 prolonged-release chewable tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí - Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1907/003 (40 mg x 30 prolonged-release chewable tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tuzulby 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tuzulby 20 mg prolonged-release chewable tablets
Tuzulby 30 mg prolonged-release chewable tablets
Tuzulby 40 mg prolonged-release chewable tablets

methylphenidate hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tuzulby is and what it is used for

Tuzulby contains the active substance methylphenidate hydrochloride. It belongs to a group of medicines which affect brain activity.

Tuzulby is to treat children and adolescents 6 to 17 years old with diagnosed attention deficit hyperactivity disorder (ADHD).
It is used in combination with complete treatment programmes (such as psychological, educational and social therapy) when such programmes alone are insufficient to control ADHD symptoms. Diagnosis should be made according to Manual of Mental disorders criteria and should be based on a complete hystory and evaluation of the child/adolescent.
Tuzulby treatment is not indicated in all children with ADHD and the decision to use the medicine must be based on the severity and persistance of symptoms considering the child´s/adolescent's age.

Tuzulby works by improving the functioning of certain parts of the brain. While it is not fully understood how the active substance in Tuzulby works, it is thought to increase levels of dopamine, a hormone that regulates mood and attention. It does this by blocking proteins in the brain which reabsorb or take back dopamine into the nerves. This helps improve attention and concentration and can help control impulsive behaviour.

2. What you or your child need to know before you or your child take Tuzulby

Do not take Tuzulby if you or your child
- are allergic to methylphenidate or any of the other ingredients of this medicine (listed in section 6)
- have an overactive thyroid gland (hyperhtyroidism) or abnormally high blood levels of thyroid hormones (thyrotoxicosis)
- are currently taking monoamine oxidase (MAO) inhibitors (a medicine for depression) or have taken these within the last 14 days – see 'Other medicines and Tuzulby'
- have glaucoma (increased pressure in your eye)
- have a phaeochromocytoma (a tumour of your adrenal gland)

- have very high blood pressure or arterial occlusive disease (narrowing of the blood vessels)
- have heart problems (such as a heart attack, severe abnormal or irregular heartbeat (arrhythmia) or disorders caused by channels that control electrical activity (channelopathies), pain and discomfort in the chest (angina), heart failure, heart disease, damage to the heart muscle [cardiomyopathy])
- have or have had a problem with the blood vessels in your brain (such as a stroke, aneurysm [swelling and weakening of part of a blood vessel], narrowed or blocked blood vessels, or vasculitis [inflammation of the blood vessels])
- have or had mental health problems, such as:
    - severe depression, suicidal thoughts
    - eating disorder, such as anorexia nervosa or other anorexic disorder
    - psychosis (a severe mental disorder in which a person loses the ability to recognise reality or relate to others), psychopathic or borderline personality disorder
    - severe mood disorder, mania
    - insufficiently controlled current or previously diagnosed severe and episodic bipolar disorder.

Do not take methylphenidate if any of the above apply to you or your child. If you are not sure, talk to your doctor or pharmacist before you take methylphenidate.

Warnings and precautions
Talk to your doctor before taking Tuzulby if you have:
- Long term use in children and adolescents: re-evaluation the long term usedulness of the medicine to assess the patient functioning.
- Cardiovascular disease: conditions affecting the heart and blood circulation, including any family history of sudden or unexplained death or serious heart rhythm problems. Your doctor will do a careful assessment before you start treatment with Tuzulby, including tests and a review of your and your family's medical history, to check for heart disease or serious heart rhythm problems. Your doctor will also check your blood pressure and pulse regularly during treatment, especially when adjusting the dose, and at least every 6 months.
- There have been reports of sudden death in children taking stimulants at normal doses, especially those with serious heart problems or structural heart abnormalities. Stimulant medicines are not recommended for children or teenagers with known serious heart conditions, as these could increase the risk of sudden death.
- If you develop symptoms of heart disease during treatment with Tuzulby such as palpitations, chest pain during exercise, fainting or shortness of breath, tell your doctor immediately.
- Cerebrovascular disorders; neurological signs and symptoms should be assessed after initiation of treatment with methylphenidate.
- Psychiatric disorders; they should be monitored at every dose adjustment.
- Worsening of psychotic or mania symptoms.
- Emergency of new psychotic or mania symptoms.
- Aggressive or hostile behaviour.
- Suicidal tendency.
- Tics.
- Anxiety, agitation or tension.
- Form of bipolar disorders.
- Effects on growth.
- Seizures.
- Abuse, misuse and diversion.
- Withdrawal.

During treatment, male children and adolescents may unexpectedly experience prolonged erections. This may be painful and can occur at any time. It is important to contact your doctor straight away if your erection lasts for longer than 2 hours, particularly if this is painful.

Tell your doctor or pharmacist if any of the above apply to you before starting treatment. This is because methylphenidate can make these problems worse. Your doctor will want to monitor how the medicine affects you.

If Tuzulby is not used properly, this may cause abnormal behaviour. It may also mean that you start to depend on the medicine. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

Checks that your doctor will make before you start taking methylphenidate
These checks are to decide if methylphenidate is the correct medicine for you. Your doctor will talk to you about:
- any other medicines you are taking
- whether there is any family history of sudden unexplained death
- any other medical problems (such as heart problems) you or your family may have
- how you are feeling, such as feeling high or low, having strange thoughts or if you have had any of these feelings in the past
- whether there is a family history of 'tics' (hard-to-control, repeated twitching of any parts of the body or repeating sounds and words)
- any mental health or behaviour problems you or other family members have ever had. Your doctor will discuss whether you are at risk of having mood swings (from being manic to being depressed called 'bipolar disorder'). They will check your mental health history, and check if any of your family have a history of suicide, bipolar disorder or depression.

It is important that you provide as much information as you can. This will help your doctor decide if methylphenidate is the correct medicine for you. Your doctor may decide that other medical tests are needed before you start taking this medicine.

Use in adults and elderly patients
Methylphenidate is not indicated for use in adults with ADHD.
Methylphenidate should not be used in elderly patients.
Safety and efficacy have not been established in these age groups.

Use in children under 6 years of age
Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy have not been established in these age groups.

Other medicines and Tuzulby
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Methylphenidate may affect how well other medicines work or may cause side effects when used in combination with certain medicines. It may, therefore, be necessary to change the dose of the medicine or to stop the medicine altogether if you are taking other medicines. Check with your doctor or pharmacist before taking methylphenidate if you are taking:
- medicines for depression
- medicines for severe mental health problems (e.g. against schizophrenia)
- medicines for epilepsy
- medicines used to reduce or increase blood pressure
- some cough and cold remedies which contain medicines that can affect blood pressure. It is important to check with your pharmacist when you buy any of these products
- medicines that thin the blood to prevent blood clots
- alcohol
- medicines acting as central alpha-2 agonist (e.g. clonidine)

If you are in any doubt about whether any medicines you are taking are included in the list above, ask your doctor or pharmacist before taking methylphenidate.

Having a surgery
Tell your doctor if you are going to have a surgery. You should not take methylphenidate on the day of your surgery if halogenated anaesthetics (a type of anaesthetic) are used. This is because there is a chance of a sudden rise in blood pressure and heart rate during the surgery.

Drug testing

This medicine may give a positive result when testing for drug use. This includes testing used in sport.

Taking Tuzulby with food, drink and alcohol
Do not drink alcohol while taking this medicine. Alcohol may make the side effects of this medicine worse.

Pregnancy, breast-feeding
Methylphenidate should not be used during pregnancy unless your doctor considers the benefits of taking this medicine outweigh the risks for the unborn baby.
Do not breast-feed while taking Tuzulby unless you are told to do so by your doctor.

If you are breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving or using machines
You may feel dizzy, have problems focussing or have blurred vision when taking methylphenidate. If these happen it may be dangerous to do things such as drive, use machines, ride a bike or horse or climb trees.

This medicinal product contains aspartame
Each 20 mg chewable tablet contains 6.1 mg of aspartame (E 951).
Each 30 mg chewable tablet contains 9.15 mg of aspartame (E 951).
Each 40 mg prolonged-release chewable tablet contains 12.2 mg of aspartame (E 951).
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.

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

3. How to take Tuzulby

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment must be under the supervision of a specialist in childhood behavioural disorders.

- Your doctor will usually start treatment with a low dose (20 mg) and increase it gradually as required. The maximum daily dose is 60 mg.
- If you are already taking immediate-release methylphenidate, your doctor may prescribe an equivalent dose of Tuzulby (prolonged-release methylphenidate) instead.
- Take Tuzulby once daily. Tuzulby can be taken with or without food. Tuzulby is a prolonged-release chewable tablet. This means that after taking the tablet, the medicine is released into your body throughout the day.
- The tablets should be chewed.
- Taking methylphenidate with food may help to stop stomach pains, feeling sick or being sick.
- The 20 mg and 30 mg Tuzulby chewable tablets are scored (bisected) and can be cut. Tuzulby 20 mg and 30 mg can be divided into equal doses.

Do not swallow the dessicant canister provided in the bottle.

Long-term treatment
If you take Tuzulby for more than a year, your doctor should pause treatment for a short time to check of the medicine is still needed. This may be planned during a school holiday. Improvements seen when taking the medicine may persevere once the medicine is stopped.

If you take more Tuzulby than you should
Taking too much Tuzulby may lead to serious side effects involving the nervous system. If you take too much medicine, talk to a doctor or call an ambulance straight away. Tell them how much of the medicine you have taken.

Signs of an overdose may include: being sick, feeling agitated, shaking, increased uncontrolled movements, muscle twitching, fits (may be followed by coma), feeling very happy, being confused, seeing, feeling or hearing things that are not real (hallucinations), sweating, flushing, headache, high fever, changes in heart beat (slow, fast or uneven), high blood pressure, dilated pupils, dry nose and mouth, muscle spasms, fever, red-brown urine which could be possible signs of abnormal breakdown of muscles (rhabdomyolysis). If you notice any of these symptoms, call your doctor immediately.

If you forget to take Tuzulby
Do not take a double dose to make up for a forgotten dose. If you forget a dose, wait until it is time for the next dose.

If you stop taking Tuzulby
If you suddenly stop taking this medicine, the ADHD symptoms may come back or unwanted effects such as depression may appear. Your doctor may want to gradually reduce the amount of medicine taken each day, before stopping it completely. Talk to your doctor before stopping Tuzulby.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will talk to you about these side effects.

Some side effects could be serious. If you have any of the side effects below, see a doctor straight away:
Common (may affect up to 1 in 10 people)
- uneven heartbeat (palpitations, tachycardia, arrhythmia).
- mood changes or mood swings or changes in personality.

Uncommon (may affect up to 1 in 100 people)
- thinking about or feeling like killing yourself (suicidal tendency).
- suicide.
- feeling, or hearing things that are not real, these are signs of psychosis.
- uncontrolled speech and body movements (Tourette's), emotional poverty.
- signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, urticaria, pruritis.

Rare (may affect up to 1 in 1 000 people)
- feeling unusually excited, over-active and un-inhibited (mania).

Very rare (may affect up to 1 in 10 000 people)
- heart attack, myocardial infarction.
- fits (seizures, convulsions epilepsy).
- skin peeling or purplish red patches, erythema multiforme.
- muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system - due to a temporary lack of blood supply to the brain.
- paralysis or problems with movement and vision, difficulties in speech; these can be signs of problems with the blood vessels in your brain.
- decrease in number of blood cells (red cells, white cells and platelets) which can make you more likely to get infections, and make you bleed and bruise more easily and decrease of white cells.

- a sudden increase in body temperature, very high blood pressure and severe convulsions ('Neuroleptic Malignant Syndrome'). It is not certain that this side effect is caused by methylphenidate or other medicines that may be taken in combination with methylphenidate.

Not known (frequency cannot be estimated from the available data)
- unwanted thoughts that keep coming back.
- unexplained fainting, chest pain, shortness of breath; these can be signs of heart problems.
- inability to control the excretion of urine (incontinence).
- spasm of the jaw muscles making it difficult to open the mouth (trismus).
- Stuttering.

If you have any of the side effects above, see a doctor straight away.

Other side effects include the following, if they get serious, please tell your doctor or pharmacist:
Very common (affects more than 1 in 10 people)
- decreased appetite.
- headache.
- feeling nervous (nervousness).
- not being able to sleep (insomnia).
- nausea.
- dry mouth.

Common (may affect up to 1 in 10 people)
- joint pain (arthralgia).
- high temperature (fever).
- unusual hair loss or thinning.
- feeling unusually sleepy or drowsy.
- loss of appetite (anorexia).
- panic attacks.
- reduced sex drive.
- toothache.
- excessive teeth grinding (bruxism).
- nasopharyngitis.
- itching, rash or raised red itchy rashes (hives).
- excessive sweating.
- cough, sore throat or nose and throat irritation, shortness of breath or chest pain.
- changes in blood pressure (usually high blood pressure, fast heart beat (tachycardia), cold hands and feet.
- shaking or trembling,feeling dizzy, movements which you cannot control, being unusually active
- feeling aggressive, agitated, anxious, depressed, irritable and abnormal behaviour, sleep problems, fatigue.
- stomach pain, diarrhoea, feeling sick, stomach discomfort and being sick.
  These usually occur at the beginning of treatment and may be reduced by taking the medicine with food.

Uncommon (may affect up to 1 in 100 people)
- constipation.
- chest discomfort.
- blood in the urine (haematuria).
- double vision or blurred vision (diplopia).
- muscle pain, muscle twitching, muscle tension.
- increases in liver test results (seen in a blood test).
- anger, feeling restless or tearful, excessive awareness of surroundings, tension.
- sedation, decreased appetite.
- exfoliative conditions.
- cardiac murmur.

Rare (may affect up to 1 in 1,000 people)
- changes in sex drive.
- feeling disorientated.
- dilated pupils, trouble seeing.
- angina pectoris.
- swelling of the breasts in men (gynaecomastia).
- redness of the skin, red raised skin rash.

Very rare (may affect up to 1 in 10,000 people)
- heart attack.
- sudden death.
- muscle cramps.
- small red marks on the skin.
- inflammation or blocked arteries in the brain.
- abnormal liver function including liver failure and coma.
- changes in test results – including liver and blood tests.
- suicidal attempt, abnormal thinking, lack of feeling or emotion, doing things over and over again, being obsessed with one thing.
- fingers and toes feeling numb, tingling and changing colour (from white to blue, then red) when cold ('Raynaud's phenomenon').

Not known (frequency cannot be estimated from the available data)
- migraine.
- very high fever.
- slow, fast or extra heart beats.
- a major fit ('grand mal convulsions'), migraine.
- believing things that are not true, confusion, delusions.
- severe stomach pain, often with feeling and being sick.
- problems with the blood vessels of the brain (stroke, cerebral arteritis or cerebral occlusion).
- erectile dysfunction, permanent erections, which are sometimes painful, or more frequent erections.
- Blood cells disorders (increased and drecreased).
- excessive uncontrolled talking.
- Pancytopenia.

Effects on growth
When used for more than a year, methylphenidate may cause reduced growth in some children and adolescents. This affects less than 1 in 10 children.
- There may be lack of weight gain or height growth.
- Your doctor will carefully watch your height and weight, as well as how well you are eating.
- If you are not growing as expected, then your treatment with methylphenidate may be stopped for a short time.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tuzulby

Keep this medicine out of the sight and reach of children.

Keep the bottle tightly closed in order to protect from moisture.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tuzulby contains

- The active substance is methylphenidate hydrochloride.

  Each 20 mg chewable tablet contains 20 mg methylphenidate hydrochloride.
  Each 30 mg chewable tablet contains 30 mg methylphenidate hydrochloride.
  Each 40 mg chewable tablet contains 40 mg methylphenidate hydrochloride.

- The other excipients are 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 flavor, talc (E 553b), silica colloidal hydrate, magnesium stearate, polyvinyl alcohol, macrogol, polysorbate 80 (E 433).

What Tuzulby looks like and contents of the pack
Tuzulby 20 mg prolonged-release chewable tablets are speckled, off white, 6.8 x 14.7 mm capsule shaped coated tablet, debossed with “N2” “N2” on one side and bisect on the other side.
The chewable tablet can be divided into equal doses.

Tuzulby 30 mg prolonged-release chewable tablets are speckled, off white, 7.7 X 16.8 mm capsule shaped coated tablet, debossed with “N3” “N3” on one side and bisect on the other side.
The chewable tablet can be divided into equal doses.

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.

Tuzulby is available in a bottle including a 2 g desiccant canister with a child-resistant cap containing 30 prolonged-release chewable tablets.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.