AUSTRALIAN PRODUCT INFORMATION – METHYLPHENIDATE-TEVA XR (METHYLPHENIDATE HYDROCHLORIDE) EXTENDED RELEASE TABLETS

DRUG DEPENDENCE: Methylphenidate hydrochloride extended release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 NAME OF THE MEDICINE

Methylphenidate hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

METHYLPHENIDATE-TEVA XR is available as an extended-release tablet for once-a-day oral administration containing 18, 27, 36 or 54 mg methylphenidate hydrochloride. It is designed to have a 12-hour duration of effect.

Excipient(s) with known effect: sugars (as lactose)

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

METHYLPHENIDATE-TEVA XR 18 mg are yellow film coated, capsule-shaped, biconvex tablets with “2392” printed in black ink on one side.

METHYLPHENIDATE-TEVA XR 27 mg are grey film coated, capsule-shaped, biconvex tablets with “2393” printed in black ink on one side.

METHYLPHENIDATE-TEVA XR 36 mg are white film coated capsule-shaped, biconvex tablets with “2394” printed in black ink on one side.

METHYLPHENIDATE-TEVA XR 54 mg are brownish-red film coated capsule-shaped biconvex tablets with “2395” printed in black ink on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

METHYLPHENIDATE-TEVA XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Treatment should be commenced by a specialist.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years.

Need for comprehensive treatment programme

METHYLPHENIDATE-TEVA XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational and social) for patients with

this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long term use

The effectiveness of methylphenidate hydrochloride extended release tablets for long-term use has not been systematically evaluated in controlled trials. Therefore the physician who elects to use METHYLPHENIDATE-TEVA XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

4.2 DOSE AND METHOD OF ADMINISTRATION

METHYLPHENIDATE-TEVA XR is administered orally once daily and should be taken in the morning.

METHYLPHENIDATE-TEVA XR must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

METHYLPHENIDATE-TEVA XR may be administered with or without food. Treatment should be started on the lowest possible dose.

Children (greater than 6 years old) and adolescents:

Dosage may be adjusted in 9 mg increments between 18 mg and 36 mg and consecutively in an 18 mg increment to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Adults:

Dosage can be adjusted from an initial dose of 18 or 36 mg/day in 18 mg increments to a maximum of 72 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Patients respond at different dose levels and methylphenidate hydrochloride extended release tablets must be titrated to effect on an individual patient needs and response basis.

If treatment is restarted following discontinuation then dosing will need to be re-titrated rather than restarted from the previous dose. This approach should be considered for a discontinuation period of greater than 3 months.

Patients should be reviewed at least annually to assess if there is an ongoing requirement for treatment with methylphenidate hydrochloride extended release tablets. Blood pressure and cardiovascular status should also be regularly reviewed.

Patients New to Methylphenidate

The recommended starting dose of methylphenidate hydrochloride extended release tablets for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate

The recommended dose of METHYLPHENIDATE-TEVA XR for patients who are currently taking methylphenidate three times daily at doses of 15 – 60 mg per day is provided in Table *1*.

Table 1 Recommended dose conversions

Recommended METHYLPHENIDATE-TEVA XR dose	Previous methylphenidate dose
18 mg once daily	5 mg methylphenidate three times daily
36 mg once daily	10 mg methylphenidate three times daily
54 mg once daily	15 mg methylphenidate three times daily
72 mg once daily	20 mg methylphenidate three times daily

Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate in other regimens. If improvement is not observed after appropriate dosage adjustments over a one-month period, the drug should be discontinued.

Use in Infants and children

Use of methylphenidate hydrochloride extended release tablets in patients under six years of age has not been studied in controlled trials. METHYLPHENIDATE-TEVA XR should not be used in patients under six years old.

Use in Elderly

Use of methylphenidate hydrochloride extended release tablets in patients over 65 years of age has not been studied in controlled trials

4.3 CONTRAINDICATIONS

METHYLPHENIDATE-TEVA XR is contraindicated:

- in patients with known hypersensitivity to methylphenidate or any inactive ingredient used in this product (see Section 6.1 LIST OF EXCIPIENTS);
- in patients with poorly-controlled open-angle or angle-closure glaucoma
- in combination with non-selective, irreversible monoamine oxidase (MAO) inhibitors / selective MAO-A inhibitors or within a minimum of 14 days following discontinuation of a non-selective, irreversible MAO inhibitor / selective MAO-A inhibitor (hypertensive crises may result);
- in patients with hyperthyroidism;
- in patients with severe angina pectoris;
- in patients with cardiac arrhythmia;
- in patients with phaeochromocytoma;
- in patients with known drug dependence or alcohol abuse;
- in patients with uncontrolled hypertension;
- in patients with cardiomyopathies;
- in patients with ischaemic heart disease;
- in patients with myocardial infarctions;
- in patients who currently exhibit severe depression, anorexia nervosa, psychotic-symptoms or suicidal tendency, since METHYLPHENIDATE-TEVA XR might worsen these conditions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution in the following circumstances

Drug Dependence

Methylphenidate hydrochloride extended release tablets should be given cautiously to patients with a history of drug or alcohol dependence. Chronic abusive use can lead to marked tolerance

and psychological dependence with varying degrees of abnormal behaviour. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Depression and Psychosis

Methylphenidate hydrochloride extended release tablets should not be used to treat severe depression or for the prevention or treatment of normal fatigue states. In psychotic patients administration of methylphenidate may exacerbate symptoms of behaviour disturbance and thought disorder.

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients.

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in a small minority of patients. Patients treated with methylphenidate should be monitored for the new appearance of seizures or a reduction in seizure-control. If the seizure frequency increases following the initiation of methylphenidate, consideration should be given to discontinuation of the drug.

Potential for Gastrointestinal Obstruction

Methylphenidate hydrochloride extended release tablets is non-deformable and does not appreciably change in shape in the GIT. It should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. Due to the prolonged-release design of the tablet, methylphenidate hydrochloride extended release tablets should only be used in patients who are able to swallow the tablet whole.

Increased intraocular pressure and glaucoma

There have been reports of a transient elevation of intraocular pressure (IOP) associated with methylphenidate treatment. It is recommended to prescribe methylphenidate hydrochloride extended release tablets to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Patients with a history of abnormally increased IOP or open- angle glaucoma, and patients at risk for acute angle-closure glaucoma (e.g., patients with significant hyperopia) must be closely monitored.

Methylphenidate hydrochloride extended release tablets is not recommended in patients with angle-closure glaucoma.

Methylphenidate hydrochloride extended release tablets is contraindicated in all patients with poorly controlled glaucoma (see Section 4.3 CONTRAINDICATIONS).

Motor and verbal tics and worsening of Tourette's syndrome

Methylphenidate has been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. It is recommended that the family history be assessed, and that the patient is clinically evaluated for tics or Tourette's syndrome before initiating methylphenidate. Regular monitoring for the emergence or worsening of tics or Tourette's syndrome during treatment with methylphenidate is recommended at every dose

adjustment and every visit, and treatment discontinued if clinically appropriate.

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents:

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults:

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

It is essential that children, adolescents, or adults with pre-existing structural cardiac abnormalities or other serious heart problems being considered for treatment are assessed by a cardiologist before initiating treatment. Ongoing cardiologist supervision should be maintained throughout treatment in these patients.

Hypertension and Other Cardiovascular Conditions

Children, adolescents or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

In the laboratory clinical trials in children, both methylphenidate hydrochloride extended release tablets and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In placebo-controlled studies in adults, mean increases in resting pulse rate of approximately 4 to 6 bpm were observed with methylphenidate hydrochloride extended release tablets at endpoint vs. a mean change of roughly -2 to 3 bpm with placebo. Mean changes in blood pressure at endpoint ranged from about -1 to 1 mm Hg (systolic) and 0 to 1 mm Hg (diastolic) for methylphenidate hydrochloride extended release tablets and from -1 to 1 mm Hg (systolic) and -2 to 0 mm Hg (diastolic) for placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. Blood pressure and cardiovascular status should be reviewed regularly during treatment with methylphenidate hydrochloride extended release tablets.

Aggression, anxiety and agitation

Aggressive behaviour, marked anxiety or agitation are often observed in patients with ADHD, and have been reported in patients treated with methylphenidate hydrochloride extended release tablets (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Anxiety led to

discontinuation of methylphenidate hydrochloride extended release tablets in some patients. It is recommended that patients be monitored for the appearance of, or worsening of, aggressive behaviour, marked anxiety, or agitation, at the beginning of treatment with methylphenidate hydrochloride extended release tablets, following every dose adjustment, and regularly during continued treatment at a steady dose.

Priapism

Prolonged and painful erections requiring immediate medical attention (sometimes including surgical intervention, have been reported with methylphenidate products, including methylphenidate hydrochloride extended release tablets, in both paediatric and adult patients (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Priapism can develop after some time on methylphenidate, often subsequent to an increase in dose. Priapism has also appeared during a period of methylphenidate withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained erections or frequent and painful erections should seek immediate medical attention.

Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including methylphenidate hydrochloride extended release tablets, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, have been observed in postmarketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Cerebrovascular disorders

Cerebrovascular disorders (including cerebral vasculitis and cerebral haemorrhage) have been reported with the use of methylphenidate hydrochloride extended release tablets (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Consider cerebrovascular disorders as a possible diagnosis in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate hydrochloride extended release tablets therapy. These symptoms could include severe headache, unilateral weakness or paralysis, and impairment of coordination, vision, speech, language, or memory. If a cerebrovascular disorder is suspected during treatment, discontinue methylphenidate hydrochloride extended release tablets immediately. Early diagnosis may guide subsequent treatment.

In patients with pre-existing cerebrovascular disorders (e.g., aneurysm, vascular malformations/anomalies), treatment with methylphenidate hydrochloride extended release tablets is not recommended**.**

Haematologic Monitoring

Periodic full blood count, differential and platelet counts are advised during prolonged therapy.

Long-term Suppression of Growth

Careful follow-up of weight and height in children aged 7 to 10 years who were randomised to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over

3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Instructions to the patient

METHYLPHENIDATE-TEVA XR must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided or crushed. The medication is contained within a non-absorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Use in hepatic impairment

There is no experience with the use of methylphenidate hydrochloride extended release tablets in patients with hepatic insufficiency.

Use in renal impairment

There is no experience with the use of methylphenidate hydrochloride extended release tablets in patients with renal insufficiency. After oral administration of radiolabelled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of METHYLPHENIDATE-TEVA XR.

Use in the elderly

No data available.

Paediatric use

The safety and efficacy of methylphenidate hydrochloride extended release tablets in children under 6 years old have not been established.

Long-term effects of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e. weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Effects on laboratory tests

See **"**Haematologic Monitoring**"** above.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Methylphenidate hydrochloride extended release tablets should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors (see Section 4.3 CONTRAINDICATIONS).

Because of possible effects on blood pressure, methylphenidate hydrochloride extended release

tablets should be used cautiously with vasopressor agents.

Coadministration of methylphenidate with anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors) has occasionally been reported to lead to serious adverse effects. Patients should be monitored for adverse events during concomitant use. Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate, and it may be necessary to monitor plasma drug concentrations of anticonvulsants and tricyclic antidepressants.

Methylphenidate hydrochloride extended release tablets may decrease the effectiveness of drugs used to treat hypertension. It is recommended to monitor blood pressure and adjust the dosage of the antihypertensive drug as needed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concomitant use of halogenated anaesthetics and Methylphenidate hydrochloride extended release tablets may increase the risk of sudden blood pressure and heart rate increase during surgery. It is recommended to avoid use of Methylphenidate hydrochloride extended release tablets in patients being treated with anaesthetics on the day of surgery.

There have been reports of serotonin syndrome following coadministration of methylphenidate with serotonergic drugs. If concomitant use of methylphenidate hydrochloride extended release tablets with a serotonergic drug is warranted, prompt recognition of the symptoms of serotonin syndrome is important. Methylphenidate hydrochloride extended release tablets must be discontinued as soon as possible if serotonin syndrome is suspected.

Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate hydrochloride extended release tablets may be associated with pharmacodynamic interactions when co- administered with some antipsychotics. Caution is warranted in patients receiving both methylphenidate hydrochloride extended release tablets and an antipsychotic, as extrapyramidal symptoms could emerge when these drugs are administered concomitantly or when adjusting the dosage of one or both drugs.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dietary administration of methylphenidate to male and female mice at doses up to 150– 160 mg/kg/day did not impair fertility in an 18–week continuous breeding study in which both parents and offspring were treated. This dose was approximately 7–16 fold the maximal recommended human dose on a mg/m^2 basis.

Women of child-bearing potential

Methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks (see Use in pregnancy).

Use in pregnancy

Category D

The safety of methylphenidate for use during human pregnancy has not been established. Cases of fetal cardiac malformations have been identified in large observational studies.

Methylphenidate should not be prescribed for pregnant women unless, in opinion of the physician, the potential benefits outweigh the possible risks.

Reproductive animal toxicity

Oral administration of methylphenidate to rabbits during the period of organogenesis has produced teratogenic effects at doses of 200 mg/kg/day, associated with systemic exposure (plasma AUC) approximately 5 fold that in humans receiving the maximal recommended dose. The exposure at the no-effect dose in rabbits (60 mg/kg/day) was less than human exposure. Teratogenic effects were not seen in rats at oral methylphenidate doses up to 75 mg/kg/day, associated with systemic exposure of approximately 20 fold that in humans receiving the maximal dose. Oral administration of methylphenidate to rats from early pregnancy until weaning was associated with maternal toxicity, reduced offspring weight and marginal alterations in neuromotor performance in offspring at a maternal dose of 30 mg/kg/day, approximately 3-6 fold the maximum recommended clinical dose on a mg/m^2 basis. Oral administration of methylphenidate to juvenile male and female rats at doses of 12.5 mg/kg/day or greater from weaning through mating, pregnancy and lactation until offspring weaning was associated with reduced body weight gain and motor activity in males as well as reduced offspring weight and postnatal survival. The systemic exposure (plasma AUC) was 1 to 3 fold that expected in adults or children given the maximum recommended clinical dose, while the exposure at the no-effect dose was less than clinical exposure.

Use in lactation

Oral administration of methylphenidate to rats from early pregnancy until weaning was associated with maternal toxicity, reduced offspring weight and marginal alterations in neuromotor performance in offspring at a maternal dose of 30 mg/kg/day, approximately 3-6 fold the maximum recommended clinical dose on a mg/m^2 basis. Oral administration of methylphenidate to juvenile male and female rats at doses of 12.5 mg/kg/day or greater from weaning through mating, pregnancy and lactation until offspring weaning was associated with reduced body weight gain and motor activity in males as well as reduced offspring weight and postnatal survival. The systemic exposure (plasma AUC) was 1 to 3 fold that expected in adults or children given the maximum recommended clinical dose, while the exposure at the no-effect dose was less than clinical exposure.

Methylphenidate and / or its metabolites are excreted in milk in lactating rats at similar levels to plasma level.

Methylphenidate has been detected in human milk. Caution should be exercised if methylphenidate hydrochloride extended release tablets is administered to a nursing woman; infants should be monitored in terms of irritability, sleeping difficulties and inadequate weight gain. The long-term neurodevelopmental effects of the maternal use of methylphenidate hydrochloride extended release tablets on the breastfed infant are unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that methylphenidate hydrochloride extended release tablets does not adversely affect their ability to engage in such activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Double-Blind Data – Adverse Events Reported at ≥ 1% Frequency
Adverse events (AEs) in either the paediatric or adult double-blind studies (Table 2 and Table 3) may be relevant for both patient populations.

Paediatric Patients

The safety of methylphenidate hydrochloride extended release tablets was evaluated in 639 paediatric patients (children and adolescents) with ADHD who participated in 4 placebo-controlled, double-blind clinical trials. Three of the studies were conducted in children aged 6- 12 years of age: two were cross-over studies in which patients received methylphenidate hydrochloride extended release tablets (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate and placebo for each of 7 days. The third study was a parallel group comparison in which patients were randomised to methylphenidate hydrochloride extended release tablets (doses of either 18 mg, 36 mg or 54 mg per day), immediate release methylphenidate or placebo for 28 days. In a fourth study, adolescents aged 13-18 years, receiving methylphenidate hydrochloride extended release tablets doses of 18 mg, 36 mg, 54 mg or 72 mg per day were randomised into a two week placebo-controlled, double- blind phase following an open-label 4 weeks titration phase. The information presented in this section was derived from pooled data.

Adverse Events (AEs) reported by ≥1% of methylphenidate hydrochloride extended release tablets-treated children and adolescent patients in these trials are shown in Table *2*.

Table 2 Adverse Events Reported by ≥1% of methylphenidate hydrochloride extended release tablets-Treated Children and Adolescents in 4 Placebo-Controlled, Double-Blind Clinical Trials

System/Organ Class Adverse Event	**Methylphenidate hydrochloride extended release tablets (n=321) %**	**Placebo (n=318) %**
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Psychiatric Disorders		
Insomnia*	2.8	0.3
Nervous System Disorders		
Headache	10.6	11.9
Dizziness	1.9	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal Pain	1.2	0.9
Gastrointestinal Disorders		
Abdominal Pain	6.2	3.8
Vomiting	2.8	1.6
General Disorders		
Pyrexia	2.2	0.9

*Terms of Initial insomnia (methylphenidate hydrochloride extended release tablets=0.6%) and Insomnia (methylphenidate hydrochloride extended release tablets=2.2%) are combined into Insomnia

The majority of AEs were mild to moderate in severity.

Adult Patients

The safety of methylphenidate hydrochloride extended release tablets was evaluated in 905 adult subjects with ADHD who participated in 3 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data.

Adverse Events (AEs) reported by ≥1% of methylphenidate hydrochloride extended release

tablets-treated adult subjects in these trials are shown in Table 3.

Table 3 Adverse Events Reported by ≥1% of methylphenidate hydrochloride extended *release tablets-Treated Adults subjects in 3 Placebo-Controlled, Double Blind Trials*

System Organ Class Adverse Event	**Methylphenidate hydrochloride extended release tablets.** **N=596** **(%)**	**Placebo** **N=309** **(%)**
Cardiac disorders		
Palpitations	4.5	0.6
Tachycardia	6.0	0.0
Ear and labyrinth disorders		
Vertigo	2.0	0.3
Eye disorders		
Vision blurred	1.3	1.0
Accommodation disorder	1.3	0.0
Gastrointestinal disorders		
Constipation	1.5	0.6
Dry mouth	15.1	3.6
Dyspepsia	2.0	1.9
Nausea	14.3	4.9
Vomiting	1.8	0.6
General disorders and administration site conditions		
Fatigue	4.7	4.2
Irritability	5.2	2.9
Thirst	1.8	0.6
Asthenia	1.2	0.0
Infections and infestations		
Influenza	8 (1.9)	4 (1.9)
Nasopharyngitis	19 (4.6)	11 (5.2)
Upper respiratory tract infection	1.7	1.0
Sinusitis	1.3	1.0
Investigations		
Blood pressure increased	2.5	1.9
Heart rate increased	3.0	1.9
Weight decreased	8.7	3.6
Alanine aminotransferase increased	1.0	0.0
Metabolism and nutrition disorders		
Anorexia	4.2	1.3
Decreased appetite	24.8	6.1
Musculoskeletal and connective tissue disorders		
Muscle tightness	1.3	0.0
Muscle spasms	1.0	0.3
Myalgia	5 (1.2)	3 (1.4)
Nervous system disorders		

Dizziness	7.4	5.5
Headache	24.2	18.8
Paraesthesia	5 (1.2)	0 (0.0)
Somnolence	7 (1.7)	9 (4.2)
Tension headache	1.0	0.3
Tremor	3.4	0.6
Psychiatric disorders		
Affect lability	1.3	0.6
Aggression	1.2	0.6
Agitation	3.2	0.6
Anxiety	8.4	2.9
Bruxism	1.5	0.6
Confusional state	1.0	0.3
Depressed mood	4.4	2.6
Depression	1.5	0.6
Initial insomnia	5.7	2.6
Insomnia	13.3	7.8
Libido decreased*	1.5	0.6
Nervousness	2.3	0.6
Restlessness	4.0	0.0
Tension	1.3	0.3
Panic attack	1.3	0.3
Cough	1.2	1.0
Oropharyngeal pain	1.5	1.3
Dyspnoea	1.2	0.6
Reproductive system and breast disorders		
Erectile dysfunction	1.0	0.3
Skin and subcutaneous tissue disorders		
Hyperhidrosis	5.7	1.3
Vascular disorders		
Hypertension	2.2	1.6
Hot flush	1.3	0.6

*The adverse reaction libido decreased includes the preferred term loss of libido

The majority of AEs were mild to moderate in severity.

Open-Label Data – Adverse Drug Reactions Reported at ≥ 1% Frequency

The safety of methylphenidate hydrochloride extended release tablets was evaluated in 3782 paediatric and adult patients with ADHD who participated in 12 open-label clinical trials. The information presented in this section was derived from pooled data.

Adverse Drug Reactions (ADRs) reported by ≥1% of methylphenidate hydrochloride extended release tablets-treated subjects in these trials and not listed in Table 2 and Table 3 are shown in Table 4.

Table 4 Adverse Drug Reactions Reported by ≥1% of methylphenidate hydrochloride extended release tablets-Treated Subjects in 12 Open-Label Clinical Trials

System/Organ Class Adverse Event	**Methylphenidate hydrochloride extended release tablets**

	(n=3782) %
General Disorders Feeling jittery	1.4
Psychiatric Disorders Tic	2.0
Mood swings	1.1
Skin and Subcutaneous Tissue Disorders Rash	1.3
Gastrointestinal disorders Diarrhoea	2.4
Abdominal discomfort	1.3
Abdominal pain	1.2

The majority of ADRs were mild to moderate in severity.

Double Blind and Open-Label Data – Adverse Drug Reactions Reported at <1% Frequency

Additional ADRs that occurred in <1% of methylphenidate hydrochloride extended release tablets-treated paediatric and adult patients in the double-blind and open-label clinical datasets are listed in Table *5*.

Table 5 Adverse Drug Reactions Reported by <1% of methylphenidate hydrochloride extended release tablets-Treated Paediatric and Adult subjects in Either Double-Blind or Open-Label Clinical Trials

Blood and Lymphatic System Disorders Leukopenia
Eye Disorders Dry eye
Investigations Cardiac Murmur
Nervous System Disorders Lethargy, Somnolence, Psychomotor Hyperactivity, Sedation
Psychiatric Disorders Depression, Anger, Hypervigilance, Sleep Disorder, Mood Altered, Agitation, Tearfulness,
Skin and Subcutaneous Tissue Disorders Rash, Rash-Macular

The majority of ADRs were mild to moderate in severity.

Post-marketing Data

Adverse events first identified as ADRs during post-marketing experience with methylphenidate hydrochloride extended release tablets are included in Table *6*. The frequencies are provided according to the following convention:

Very common ≥1/10

Common ≥1/100 and <1/10

Uncommon ≥1/1000 and <1/100

Rare ≥1/10000 and <1/1000

Very rare <1/10000, including isolated reports

Table 6 Adverse Drug Reactions Identified During Postmarketing Experience with methylphenidate hydrochloride extended release tablets by Frequency Category Estimated from Spontaneous Reporting Rates

Blood and Lymphatic System Disorders	
Very rare	Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Psychiatric Disorders	
Common	Bruxism
Rare	Aggression
Very rare	Confusional state, Disorientation, Hallucination, Hallucination Auditory, Hallucination Visual, Mania, Nervousness, Restlessness, Logorrhoea, Libido disorder*, Obsessive-compulsive disorders and symptoms (including trichotillomania, obsessive thoughts, compulsions)
Nervous System Disorders	
Very rare	Convulsion, Grand Mal Convulsion, Dyskinesia, Cerebrovascular disorder (including cerebral vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral vascular occlusion)
Eye Disorders	
Very rare	Diplopia, Mydriasis, Visual impairment
Cardiac Disorders	
Very rare	Angina Pectoris, Bradycardia, Extrasystoles, Supraventricular Tachycardia, Ventricular Extrasystoles
Vascular Disorders	
Very rare	Raynaud's Phenomenon
Respiratory, thoracic and mediastinal disorders	
Very rare	Epistaxis
Skin and Subcutaneous Tissue Disorders	
Common	Hyperhidrosis
Very rare	Alopecia, Erythema
Hepatobiliary Disorders	
Very rare	Hepatocellular injury, Acute hepatic failure
Musculoskeletal, Connective Tissue and Bone Disorders	
Very rare	Arthralgia, Myalgia, Muscle Twitching
Unknown	Trismus
Immune System Disorders	
Rare	Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions and Exanthemas NEC.
Reproductive System and Breast Disorders	
Very rare	Priapism, gynecomastia
Renal and urinary disorders	
Unknown	Incontinence
General Disorders	
Rare	Therapeutic Response Decreased
Very rare	Chest Pain, Chest Discomfort, Drug Effect Decreased, Hyperpyrexia
Investigations	
Very rare	Blood alkaline phosphatase Increased, Blood bilirubin Increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

NEC = not elsewhere classified

*The adverse reaction libido disorder includes terms apart from those associated with decreases in libido

Adverse events reported since market introduction in patients taking methylphenidate include suicide, suicide attempt, and suicide ideation. No causal relationship between methylphenidate and these events have been established.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The prolonged release of methylphenidate from methylphenidate hydrochloride extended release tablets should be considered when treating patients with overdose.

Signs and Symptoms

Signs and symptoms of methylphenidate hydrochloride extended release tablets over dosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsions, grand mal convulsions, confusional state, hallucinations (auditory and/or visual), hyperhidrosis headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmias, hypertension, mydriasis, and dry mouth.

Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. The efficacy of activated charcoal has not been established. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for methylphenidate hydrochloride extended release tablets overdosage has not been established.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Methylphenidate is a central nervous system stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Clinical trials

Children

Methylphenidate hydrochloride extended release tablets was demonstrated to be effective in the treatment of ADHD, in children aged 6 to 12 years, in three pivotal studies. Studies 1 and 2 were single-centre, double-blind, double- dummy, randomised, placebo and active-controlled,

crossover comparisons (n = 64 and 70). Study 3 was a multicentre, 4 week, double-blind, double-dummy, randomised, placebo and active-controlled, parallel study (n = 282). The primary comparison of interest in all three trials was methylphenidate hydrochloride extended release tablets versus placebo.

The primary efficacy parameter for methylphenidate hydrochloride extended release tablets was the Inattention/Overactivity with Aggression (IOWA) Conners I/O subscale rated by the community school teacher. Statistically significant ($p < 0.001$) reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for methylphenidate hydrochloride extended release tablets once daily.

Onset and duration of efficacy were assessed by the laboratory school teacher using the SKAMP (Swanson, Kotkin, Agler, M-Fynn and Pelham) combined attention ratings for studies 1 and 2. The onset of efficacy was estimated to be 1.5 hours and duration continued through to 12 hours. Patients demonstrated higher productivity and greater accuracy during methylphenidate hydrochloride extended release tablets treatment.

Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared methylphenidate hydrochloride extended release tablets administered once daily and placebo in a multi-centre, parallel group, 5-week, fixed-dose study (Study 4) (18, 36, and 72 mg/day) and in a multi-centre, parallel group, 7-week dose-titration study (Study 5) (36 to 108 mg/day).

Study 4 was a multi-centre, double-blind, randomised, placebo-controlled, parallel group, dose-response study (5-week duration) with 3 fixed dose groups (18, 36, and 72 mg). Patients were randomised to receive methylphenidate hydrochloride extended release tablets administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of methylphenidate hydrochloride extended release tablets were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

Study 5 demonstrated the effectiveness of methylphenidate hydrochloride extended release tablets in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomised to methylphenidate hydrochloride extended release tablets and 116 were randomised to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that methylphenidate hydrochloride extended release tablets was statistically significantly superior to placebo.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Methylphenidate is readily absorbed. Following oral administration of methylphenidate hydrochloride extended release tablets to adults, the drug overcoat dissolves and plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours. The methylphenidate contained in two internal drug layers is gradually released over the next few hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which plasma levels of methylphenidate gradually decrease. methylphenidate hydrochloride extended release tablets once daily minimises the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily. The extent of absorption

of methylphenidate hydrochloride extended release tablets once daily is generally comparable to conventional immediate release preparations given three times daily.

Following the administration of methylphenidate hydrochloride extended release tablets 18 mg once daily in 36 adults, the mean pharmacokinetic parameters were C_{max} 3.7 ± 1.0 ng/mL, T_{max} 6.8 ± 1.8 h, AUC_{∞} 41.8 ± 13.9 ngh/mL and $t_{1/2}$ 3.5 ± 0.4 h. No differences in the pharmacokinetics of methylphenidate hydrochloride extended release tablets were noted following single and repeated once daily dosing indicating no significant drug accumulation.

The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of methylphenidate hydrochloride 18 mg extended release tablets.

Following administration of methylphenidate hydrochloride extended release tablets in single doses of 18, 36 and 54 mg/day to adults, C_{max} and AUC_{∞} of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and AUC_{∞} increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride extended release tablets, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once daily methylphenidate hydrochloride extended release tablets doses from 54 to 144 mg/day resulted in linear and dose proportional increases in C_{max} and AUC_{∞} for total methylphenidate (MPH) and its major metabolite, (alpha)-phenyl-piperidine acetic acid (PPAA). The single dose and steady state (Day 4) clearance and half-life parameters were similar, indicating that there was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

Pharmacokinetic equivalence has been demonstrated for two 27 mg methylphenidate hydrochloride extended release tablets with three 18 mg methylphenidate hydrochloride extended release tablets. The mean values of the treatment ratio (2 x 27 mg fasted/3 x 18 mg fasted) of the log-transformed pharmacokinetic values for C_{max}, T_{max} and AUC_{∞} were 101.1%, 104.3% and 100.3% respectively. The 90% CIs for the treatment ratios were within the pre-specified 80% - 125% range.

Studies on the effects of dosing after overnight fasting, after consumption of a normal breakfast and a high-fat breakfast showed no differences in pharmacokinetics or pharmacodynamics of methylphenidate hydrochloride extended release tablets. There is no evidence of dose dumping in the presence or absence of food.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The terminal plasma half-life of methylphenidate in adults following oral administration of methylphenidate hydrochloride extended release tablets was approximately 3.5 hours.

Metabolism

In humans, methylphenidate is metabolised primarily by de-esterification to α-phenyl- piperidine acetic acid (PPAA) which has little or no pharmacologic activity. In adults the metabolism of methylphenidate hydrochloride extended release tablets once daily, as evaluated by metabolism to PPAA, is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses of methylphenidate hydrochloride extended release tablets is similar.

Excretion

After oral dosing of radiolabelled methylphenidate in humans, about 90% of the radioactivity was

recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is not expected to have a significant effect on the pharmacokinetics of methylphenidate hydrochloride extended release tablets.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Methylphenidate was not mutagenic in the in vitro assays (Ames reverse mutation assay, mouse lymphoma cell forward mutation assay). Methylphenidate was weakly clastogenic in vitro (Chinese Hamster ovary cells) but was negative in vivo (mouse bone marrow micronucleus assay). Sister chromatid exchange assay results were positive only at high (cytotoxic) concentrations.

Carcinogenicity

In a lifetime dietary carcinogenicity study carried out in mice, methylphenidate caused an increase in hepatocellular adenomas at a dose of 60–80 mg/kg/day, and in males only, an increase in hepatoblastomas (a relatively rare rodent malignant tumour type) at 60 mg/kg/day. These dose levels are approximately 3–8 fold the maximal recommended clinical dose on a mg/m^2 basis. There was no increase in tumours at 30–40 mg/kg/day (approximately 1-4 fold the maximal recommended clinical dose on a mg/m^2 basis). The mouse strain used is sensitive to the development of hepatic tumours, and the significance of these results to humans is not known. There was no evidence of carcinogenicity in two strains of transgenic mice administered methylphenidate in the diet for 24 weeks at doses up to 60–74 mg/kg/day (approximately 3– 8 fold the maximal recommended clinical dose on a mg/m^2 basis) or in a lifetime dietary study in rats at doses up to 50 mg/kg/day (approximately 4–10 fold the maximal recommended clinical dose on a mg/m^2 basis).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

METHYLPHENIDATE-TEVA XR tablets contain the following inactive ingredients:

Lactose monohydrate, hypromellose, colloidal anhydrous silica, magnesium stearate, methacrylic acid copolymer, triethyl citrate, purified talc, fumaric acid, OPACODE monogramming ink S-1-17823 Black (ARTG PI No. 12108), Opadry 85F220137 Yellow (ARTG PI No. 140409– 18 mg tablets), Opadry 85F275019 Grey (ARTG PI No. 140410– 27 mg tablets), Opadry 85F48105 White (ARTG PI No. 123056 – 37 mg tablets) and Opadry 85F15266 Red (ARTG PI No. 141465 – 54 mg tablets)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep container tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

METHYLPHENIDATE-TEVA XR tablets are supplied in round white 75 mL HDPE bottles with PP child-resistant cap containing desiccant integrated in the cap in a pack size of 30 tablets.

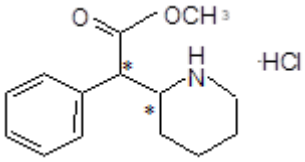
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Methylphenidate hydrochloride is the racemic mixture of d,l-*threo*-methyl *α*-phenyl-2-piperidineacetate hydrochloride. The *d*-(R,R)-isomer is pharmacologically more active than the *l*-(S,S)-isomer. Methylphenidate hydrochloride is a white, odourless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Chemical structure



$C_{14}H_{19}NO_2$.HCl

MW 269.77

CAS number

CAS-298-59-9 (methylphenidate hydrochloride)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 – Controlled Drug

8 SPONSOR

Sponsored in Australia by:

Teva Pharma Australia Pty Ltd

Level 1, 37 Epping Road

Macquarie Park NSW 2113

AUSTRALIA

9 DATE OF FIRST APPROVAL

13 October 2021

10 DATE OF REVISION

26 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Add Obsessive-compulsive disorders and symptoms as Adverse Drug Reaction