PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S6

1. NAME OF THE MEDICINE:

ACERTA 18 prolonged release tablets

ACERTA 27 prolonged release tablets

ACERTA 36 prolonged release tablets

ACERTA 54 prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ACERTA 18 prolonged release tablet contains 18 mg methylphenidate hydrochloride.

Each ACERTA 27 prolonged release tablet contains 27 mg methylphenidate hydrochloride.

Each ACERTA 36 prolonged release tablet contains 36 mg methylphenidate hydrochloride.

Each ACERTA 54 prolonged release tablet contains 54 mg methylphenidate hydrochloride.

Excipient with known effect:

ACERTA 18 contains 183,8 mg lactose (as monohydrate).

ACERTA 27 contains 184,5 mg lactose (as monohydrate).

ACERTA 36 contains 178,1 mg lactose (as monohydrate).

ACERTA 54 contains 165,3 mg lactose (as monohydrate).

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM:

Prolonged release tablets.

ACERTA 18: Capsule shaped, biconvex, yellow tablet, with ‘2392’ printed on one side in black ink.

ACERTA 27: Capsule shaped, biconvex, grey tablet, with ‘2393’ printed on one side in black ink.

ACERTA 36: Capsule shaped, biconvex, white tablet with '2394' printed on one side in black ink.

ACERTA 54: Capsule shaped, biconvex, red-brown tablet with '2395' printed on one side in black ink.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

ACERTA is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

4.2 Posology and method of administration:

Dosage should be individualised according to the need and response of each individual patient.

Patients new to methylphenidate:

The recommended starting dose of ACERTA for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults.

Patients currently using methylphenidate:

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

Table 1: Recommended dose conversion from other methylphenidate regimens to ACERTA:

Previous methylphenidate daily dose:	**Recommended ACERTA dose:**
5 mg methylphenidate hydrochloride twice daily or three times daily.	18 mg once daily.
10 mg methylphenidate hydrochloride twice daily or three times daily.	36 mg once daily.
15 mg methylphenidate hydrochloride twice	54 mg once daily.

daily or three times daily.	
20 mg methylphenidate hydrochloride twice daily or three times-daily.	72 mg once daily.

Clinical judgement should be used when selecting the dose for patients currently taking methylphenidate in other regimens.

Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day for children aged between 6 to 12 years and to a maximum of 72 mg for adolescents aged between 13 to 18 years and 108 mg in adults. In general, dosage adjustment may proceed at approximately weekly intervals.

Daily dosage above 54 mg is not recommended for children aged between 6 to 12 years.
Daily dosage above 72 mg is not recommended for adolescents aged between 13 to 18 years.
Daily dosage above 108 mg is not recommended in adults.

Maintenance/Extended Treatment:

The long-term use of ACERTA has not been systematically evaluated in controlled clinical trials. The medical practitioner who elects to use ACERTA for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the medicine for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy.

Dose reduction and discontinuation:

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, ACERTA should be discontinued.

Elderly:

Use of ACERTA in elderly patients over 65 years has not been studied in controlled trials.

Paediatric population:

Children under six years of age:

ACERTA should not be used in patients under six years old.

Method of administration:

ACERTA is administered orally once daily. As the effect has been shown to be present 12 hours after dosing, the product should be taken in the morning.

ACERTA must be swallowed whole with adequate amounts of liquids, and must not be chewed, divided, or crushed.

ACERTA may be administered with or without food.

4.3 Contraindications:

- Hypersensitivity to methylphenidate or to any of the excipients listed in **section 6.1**.
- Glaucoma.
- Phaeochromocytoma.
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicines, due to the risk of hypertensive crisis (see **section 4.5**).
- Hyperthyroidism.
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well controlled).
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the dysfunction of ion channels) and QT prolongation either congenital, familial, or caused by medication.
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including
- vasculitis or stroke.
- In patients with marked anxiety, tension, and agitation, since ACERTA may aggravate these symptoms.

- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use:

ACERTA treatment is not indicated in all children with ADHD and the decision to use the medicine must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and not simply on the presence of one or more abnormal behavioural characteristics. ACERTA should not be used for the treatment of attention-deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

Long term use (more than 12 months) in children and adolescents:

The safety and efficacy of long-term use of ACERTA has not been systematically evaluated in controlled trials. ACERTA treatment should not and need not be indefinite. ACERTA treatment is usually discontinued during or after puberty. Patients on long term therapy (i.e., over 12 months) must have careful ongoing monitoring according to the guidance in **sections 4.2** and **4.4** for cardiovascular status, growth, appetite, development of de novo or worsening of pre-existing psychiatric disorders.

Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal, and excessive perseveration.

The medical practitioner who elects to use ACERTA for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the medicine for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that ACERTA is dechallenged at least once yearly to assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

Use in the elderly:

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

Use in children under 6 years of age:

ACERTA should not be used in children under the age of 6 years (see **section 4.2**). Safety and efficacy in this age group has not been established.

Cardiovascular status:

Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant dysrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea, or other symptoms suggestive of cardiac disease during ACERTA 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 ACERTA 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. The possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data especially when treatment during childhood/adolescence is continued into adulthood. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. See **section 4.3** for conditions in which ACERTA treatment is contraindicated.

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

The use of ACERTA is contraindicated in certain pre-existing cardiovascular disorders unless specialist paediatric cardiac advice has been obtained (see **section 4.3**).

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

Sudden death has been reported in association with the use of stimulants of the central nervous

system at usual doses in children, some of whom had structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and cardiovascular events:
Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders:
See **section 4.3** for cerebrovascular conditions in which ACERTA 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 ACERTA.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate (as contained in ACERTA) 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 ACERTA and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during ACERTA therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language, or memory.

Treatment with ACERTA is not contraindicated in patients with hemiplegic cerebral palsy.

Psychiatric disorders:
Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, ACERTA should not be given.

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

Exacerbation of pre-existing psychotic or manic symptoms:

In psychotic patients, administration of ACERTA 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 ACERTA at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for ACERTA, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour:

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Aggression has been reported in patients treated with ACERTA (see **section 4.8**). Patients treated with ACERTA should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit.

Medical practitioners should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency:

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

Tics:

ACERTA has been 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 ACERTA. Patients should be regularly monitored for the emergence or worsening of tics during treatment with ACERTA. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation, or tension:

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

Forms of bipolar disorder:

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

Growth:

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

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

Growth should be monitored during ACERTA 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:

ACERTA should be used with caution in patients with epilepsy. ACERTA 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, ACERTA PR should be discontinued.

Priapism:

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

Use with serotonergic medicines:

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

Abuse, misuse, and diversion:

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

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

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

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

Withdrawal:

Careful supervision is required during ACERTA 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.

Fatigue:

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

Choice of methylphenidate formulation:

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

Drug screening:

ACERTA 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 ACERTA in patients with renal or hepatic insufficiency.

Haematological effects:

The long-term safety of treatment with ACERTA is not fully known. In the event of leukopenia, thrombocytopenia, anaemia, or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction:

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

Due to the prolonged release design of the tablet, ACERTA should only be used in patients who are able to swallow the tablet whole. Patients should be informed that ACERTA must be swallowed whole with the aid of liquids. Tablets should not be chewed, broken, divided, or crushed (see **section 4.2**). ACERTA is contained within a nonabsorbable shell designed to release the medicine at a controlled rate. The tablet shell is eliminated from the body, patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

ACERTA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ACERTA.

4.5 Interaction with other medicines and other forms of interaction:

Pharmacokinetic interaction:

It is not known how ACERTA may effect plasma concentrations of concomitantly administered medicines. Therefore, caution is recommended at combining ACERTA with other

medicines, especially those with a narrow therapeutic window.

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

Pharmacodynamic interactions:

Anti-hypertensive medicines:

ACERTA may decrease the effectiveness of medicines used to treat hypertension.

Use with medicines that elevate blood pressure:

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

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

Use with alcohol:

Alcohol may exacerbate the adverse CNS effect of psychoactive medicines, including ACERTA. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with serotonergic medicines:

There have been reports of serotonin syndrome following coadministration of ACERTA with serotonergic medicines. If concomitant use of ACERTA with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important (see **section 4.4**). ACERTA must be discontinued as soon as possible if serotonin syndrome is suspected.

Use with halogenated anaesthetics:

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, ACERTA treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g., clonidine):

The long-term safety of using ACERTA in combination with clonidine or other centrally acting alpha-2 agonists have not been systematically evaluated.

Use with dopaminergic medicines:

Caution is recommended when administering ACERTA with dopaminergic medicines, including antipsychotics. Because a predominant action of ACERTA is to increase extracellular dopamine levels, ACERTA 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:

ACERTA should not be used in pregnancy as safety has not been established.

Teratogenicity has been shown in laboratory animals.

Breastfeeding:

ACERTA is excreted in human milk. ACERTA should not be used when breastfeeding.

Fertility:

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines:

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

ACERTA can impair cognitive function and can affect a patient's ability to drive safely.

When prescribing ACERTA, patients should be told:

- ACERTA is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.

4.8 Undesirable effects:

Summary of the safety profile:

The table below shows all adverse reactions observed during clinical trials and post-market spontaneous reports with methylphenidate prolonged-release tablets and those which have been reported with other methylphenidate hydrochloride formulations. If the adverse reactions with methylphenidate prolonged-release tablet and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Tabulated list of adverse reactions:

System Organ Class	**Frequency**		
	Frequent	**Less frequent**	**Frequency unknown**
Infections and infestations	Nasopharyngitis, upper respiratory tract infection[#], sinusitis[#].		
Blood and lymphatic system disorders		Anaemia[†], leucopenia[†], thrombocytopenia, thrombocytopenic	Pancytopenia.

		purpura.	
Immune system disorders		Hypersensitivity reactions such as angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rashes, and eruptions.	
Metabolism and nutrition disorders	Anorexia, decreased appetite[†], moderately reduced weight and height gain during prolonged use in children[*].		
Psychiatric disorders	Insomnia, nervousness, affect lability, aggression[*], agitation[*], anxiety[*†], depression[*#], irritability, abnormal behaviour, mood	Psychotic disorders[*], auditory, visual, and tactile hallucination[*], anger, suicidal ideation[*], altered mood, restlessness[†], tearfulness,	Delusions[*†], thought disturbances[*], dependence, cases of abuse and dependence have been described, more often with immediate release formulations.

	swings, tics*, initial insomnia#, depressed mood#, decreased libido#, tension#, bruxism^, panic attack#.	worsening of pre-existing tics of Tourette's syndrome*, logorrhoea, hypervigilance, sleep disorder, mania*†, disorientation, libido disorder, confusional state†, suicidal attempt (including completed suicide)*†, transient depressed mood*, abnormal thinking, apathy†, repetitive behaviours, over-focussing.	
Nervous system disorders	Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, paresthaesia#, tension headache#.	Convulsion, choreoathetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS; reports were poorly documented, and, in most cases,	Cerebro-vascular disorders*† (including vasculitis, cerebral haemorrhages, cerebro-vascular accidents, cerebral arteritis, cerebral occlusion), Grand mal convulsion*, migraine†, dysphemia.

		patients were also receiving other medicines, so the role of methylphenidate is unclear), sedation, tremor†, lethargy#.	
Eye disorders	Accommodation disorder#.	Blurred vision†, dry eye#, difficulties in visual accommodation, visual impairment, diplopia.	Mydriasis.
Ear and labyrinth disorders	Vertigo#.		
Cardiac disorders	Dysrhythmia, tachycardia, palpitations.	Chest pain, angina pectoris, cardiac arrest; myocardial infarction.	Supra-ventricular tachycardia, bradycardia, ventricular extrasystoles†, extrasystoles†.
Vascular disorders	Hypertension.	Hot flush#, cerebral arteritis and/or occlusion, peripheral coldness†, Raynaud's phenomenon.	
Respiratory,	Cough,	Dyspnoea†.	Epistaxis.

thoracic, and mediastinal disorders	oropharyngeal pain.		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, nausea†, abdominal discomfort, vomiting, dry mouth†, dyspepsia#.	Constipation†.	
Hepato-biliary disorders	Increased alanine aminotransferase# .	Increased hepatic enzymes, abnormal liver function, including acute hepatic failure and hepatic coma, increased blood alkaline phosphatase, increased blood bilirubin†.	
Skin and subcutaneous tissue disorders	Alopecia, rash, pruritis, urticaria, hyperhidrosis†	Angioedema, bullous conditions, exfoliative conditions, macular rash, erythema, erythema multiforme, exfoliative dermatitis, fixed	

		drug eruption.	
Musculoskeletal and connective tissue disorders	Arthralgia, muscle tightness#, muscle spasms#.	Myalgia†, muscle twitching, muscle cramps.	Trismus^
Renal and urinary disorders		Haematuria, pollakiuria.	Incontinence.
Reproductive system and breast disorders	Erectile dysfunction#.	Gynaecomastia.	Priapism*, increased erection* and prolonged erection*.
General disorders and administration site conditions	Pyrexia, growth retardation during prolonged use in children*, fatigue†, irritability#, feeling jittery#, asthenia#, thirst#.	Chest pain, sudden cardiac death*	Chest discomfort†, hyperpyrexia, decreased therapeutic response, decreased medicine effect.
Investigations	Changes in blood pressure and heart rate (usually an increase)*, decreased weight*.	Cardiac murmur*, decreased platelet count, abnormal white blood cell count.	

* See **section 4.4**

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

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

^ Based on the frequency calculated in adult ADHD studies (no cases were reported in the paediatric studies).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from formulations with extended durations of action.

Signs and symptoms:

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac dysrhythmias, hypertension, mydriasis, dryness of mucous membranes and rhabdomyolysis.

Treatment:

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

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

Intensive care must be provided to maintain adequate circulation and respiratory exchange.

external cooling procedures may be required for hyperpyrexia.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

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

Mechanism of action:

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

5.2 Pharmacokinetic properties:

Absorption:

Methylphenidate is readily absorbed. Following oral administration of methylphenidate prolonged release tablets to adults the tablet coating dissolves, providing an initial maximum methylphenidate concentration at about 1 to 2 hours. The methylphenidate contained in the tablet core is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease.
Methylphenidate prolonged release tablets taken once daily minimises the fluctuations between peak and trough concentrations associated with immediate release methylphenidate three times daily. The extent of absorption of methylphenidate prolonged release tablets once daily is generally comparable to conventional immediate release preparations.
The mean pharmacokinetic parameters in 36 adults following the administration of extended-release methylphenidate 18 mg once daily are summarised in **Table 2.**

Table 2.

Mean ± SD Pharmacokinetic Parameters	
PARAMETERS	**Extended-release methylphenidate (18 mg once daily) (n=36)**
C_{max} (ng/mL)	3,7 ± 1,0
T_{max} (h)	6,8 ± 1,8
AUG_{inf} (ng·h/mL)	41,8 ± 13,9
$t_{1/2}$ (h)	3,5 ± 0,4

No differences in the pharmacokinetics of methylphenidate prolonged release tablets were noted following single and repeated once daily dosing, indicating no significant methylphenidate accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of methylphenidate prolonged release tablets 18 mg.

Following administration of methylphenidate prolonged release tablets in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC_{inf} of methylphenidate were proportional to dose.

Distribution:

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of methylphenidate prolonged release tablets were approximately 3,5 h. The rate of protein binding of methylphenidate and of its metabolites is approximately 15 %. The apparent volume of distribution of methylphenidate is approximately 13 litres/kg.

Biotransformation:

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

Elimination:

The elimination half-life of methylphenidate in adults following administration of methylphenidate prolonged release tablets were approximately 3,5 hours. After oral administration, about 90 % of the dose is excreted in urine and 1 to 3 % in faeces, as metabolites within 48 to 96 hours. Small quantities of unchanged methylphenidate are recovered in urine (less than 1 %). The main urinary metabolite is alpha-phenyl-piperidine acetic acid (60 to 90 %).

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

Food Effects:

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

Special populations:

Gender:

In healthy adults, the mean dose adjusted AUC_{inf} values for methylphenidate prolonged release tablets were 36,7 ng.h/mL in men and 37,1 ng.h/mL in women, with no differences noted between the two groups.

Age:

The pharmacokinetics of extended-release methylphenidate has not been studied in children less than 6 years of age.

Renal Insufficiency:

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

Hepatic Insufficiency:

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

5.3 Preclinical safety data:

Carcinogenicity:

In 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-embryonal/foetal development:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet content:

Fumaric acid

Hypromellose

Lactose monohydrate

Magnesium stearate

Methacrylic acid–methyl methacrylate copolymer

Silica, colloidal anhydrous

Triethyl citrate

Talc

Tablet coating:

18 mg prolonged release tablets:

Iron oxide red (E172)

Iron oxide yellow (E172)

Polyvinyl alcohol, part hydrolysed

Macrogol (3350)

Talc

Titanium dioxide (E171)

27 mg prolonged release tablets:

Indigo carmine aluminium lake (E132)

Iron oxide black (E172)

Iron oxide yellow (E172)

Polyvinyl alcohol, part hydrolysed

Macrogol (3350)

Talc

Titanium dioxide (E171)

36 mg prolonged release tablets:

Macrogol (3350)

Polyvinyl alcohol, part hydrolysed

Talc

Titanium dioxide (E171)

54 mg prolonged release tablets:

Iron oxide red (E172)

Macrogol (3350)

Polyvinyl alcohol, part hydrolysed

Talc

Titanium dioxide (E171)

Printing ink:

Iron oxide black (E172)

Isopropyl alcohol

Shellac glaze

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

18 mg tablets: 24 months

27 mg tablets: 24 months

36 mg tablets: 24 months

54 mg tablets: 24 months

Shelf life after first opening the bottle:

18 mg tablets: 3 months

27 mg tablets: 6 months

36 mg tablets: 6 months

54 mg tablets: 6 months

6.4 Special precautions for storage:

Store at or below 30 °C.

Store in the original packaging until required for use.

Keep the container tightly closed.

6.5 Nature and contents of container:

The tablets are packaged in white, round HDPE containers closed with child resistant polypropylene closure with gel desiccant integrated in the cap.

Pack sizes:

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

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

36 mg tablets: 28, 30 or 100 prolonged release tablets.

54 mg tablets: 28, 30 or 100 prolonged release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER:

ACERTA 18: 51/1.2/0285

ACERTA 27: 51/1.2/0286

ACERTA 36: 51/1.2/0287

ACERTA 54: 51/1.2/0288

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

8 December 2020

10. DATE OF REVISION OF THE TEXT:

28 October 2024