Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Approved Professional Information for Medicines for Human Use:

ATEROCON LA

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

ATEROCON LA 10 mg modified-release hard capsules

ATEROCON LA 20 mg modified-release hard capsules

ATEROCON LA 30 mg modified-release hard capsules

ATEROCON LA 40 mg modified-release hard capsules

ATEROCON LA 60 mg modified-release hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ATEROCON LA 10 mg modified-release hard capsules

Each modified-release capsule contains 8,65 mg methylphenidate as 10 mg methylphenidate hydrochloride.

ATEROCON LA 20 mg modified-release hard capsules

Each modified-release capsule contains 17,3 mg methylphenidate as 20 mg methylphenidate hydrochloride.

ATEROCON LA 30 mg modified-release hard capsules

Each modified-release capsule contains 25,95 mg methylphenidate as 30 mg methylphenidate hydrochloride.

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ATEROCON LA 40 mg modified-release hard capsules

Each modified-release capsule contains 34,6 mg methylphenidate as 40 mg methylphenidate hydrochloride.

ATEROCON LA 60 mg modified-release hard capsules

Each modified-release capsule contains 51,9 mg methylphenidate as 60 mg methylphenidate hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsule, hard.

ATEROCON LA 10 mg modified-release hard capsules

Opaque hard gelatine capsule (size 3) with orange cap and white body imprinted “10” with black ink, filled with white to off-white spherical pellets. Capsule length: 15,9 mm.

ATEROCON LA 20 mg modified-release hard capsules

Opaque hard gelatine capsule (size 3) with white cap and white body, imprinted “20” with black ink, filled with white to off-white spherical pellets. Capsule length: 15,9 mm.

ATEROCON LA 30 mg modified-release hard capsules

Opaque hard gelatine capsule (size 2) with yellow cap and yellow body, imprinted “30” with black ink, filled with white to off-white spherical pellets. Capsule length: 18 mm.

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ATEROCON LA 40 mg modified-release hard capsules

Opaque hard gelatine capsule (size 1) with orange cap and orange body, imprinted “40” with black ink, filled with white to off-white spherical pellets. Capsule length: 19,4 mm.

ATEROCON LA 60 mg modified-release hard capsules

Opaque hard gelatine capsule (size 0) with yellow cap and white body imprinted “60” with black ink, filled with white to off-white spherical pellets. Capsule length: 21,7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Attention deficit hyperactivity disorder (ADHD) in children aged 6 years or older, and in adults with ADHD onset in childhood.

The diagnosis should be made according to current DSM criteria or the guidance from International Classification of Diseases (ICD).

4.2 Posology and method of administration

Posology

The dosage of ATEROCON LA should be individualised according to the patient’s clinical needs and responses.

ATEROCON LA should be started at a low dose, with increments at weekly intervals.

Daily doses above 60 mg are not recommended for the treatment of ADHD in children.

Effective doses in adults may vary and range from 40 – 80 mg per day.

Daily doses above 80 mg are not recommended for the treatment of ADHD in adults (ATEROCON LA only).

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

If paradoxical aggravation of symptoms or other adverse effects occur, ATEROCON LA should be discontinued.

Pre-treatment screening

Before initiating ATEROCON LA treatment, patients should be assessed for pre-existing cardiovascular and psychiatric disorders and a family history of sudden death, ventricular dysrhythmia and psychiatric disorders (see sections 4.3, 4.4 and 4.5).

Periodic assessment of the treatment in ADHD

Medicine treatment should not and need not be indefinite.

ATEROCON LA should be periodically discontinued to assess the patient's condition. Improvement may be sustained when the medicine is either temporarily or permanently discontinued.

When used in children with ADHD, ATEROCON LA can usually be discontinued after puberty.

ADHD

Children and adolescents (6 years and over)

ATEROCON LA (methylphenidate hydrochloride modified-release capsules) is for oral administration once daily in the morning.

The recommended starting dose of ATEROCON LA is 20 mg. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with ATEROCON LA 10 mg.

Daily dosage above 60 mg is not recommended.

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Adults

Only the ATEROCON LA prolonged release and not methylphenidate immediate release formulations should be used for the treatment of ADHD in adults.

ATEROCON LA is administered once daily in the morning.

Patients new to methylphenidate

The recommended starting dose of ATEROCON LA in patients who are not currently taking methylphenidate is 20 mg once daily.

Patients currently using methylphenidate

Treatment may be continued with the same daily dose. If the patient was previously treated with an immediate release formulation, a conversion to an appropriate recommended dose of ATEROCON LA should be made (see below subsection "Switching patients to ATEROCON LA").

A maximum daily dose of 80 mg should not be exceeded.

Switching patients to ATEROCON LA

The recommended dose of ATEROCON LA should be equal to the total daily dose of the immediate release formulations not exceeding a total of 60 mg in children and 80 mg in adults. An example in patients being switched from the immediate-released formulation is provided below.

Recommended daily dose when switching patients from an Immediate Release (IR) methylphenidate dose to ATEROCON LA

Previous IR methylphenidate dose	Recommended ATEROCON LA dose
5 mg twice daily	10 mg once daily

10 mg twice daily	20 mg once daily
15 mg twice daily	30 mg once daily
20 mg twice daily	40 mg once daily

For other ATEROCON LA regimens, clinical judgment should be used when selecting the starting dose. ATEROCON LA dosage may be adjusted at weekly intervals in 10 mg increments for children and in 20 mg increments for adults

Special populations

Elderly

ATEROCON LA should not be used in the elderly. Safety and efficacy have not been established in ADHD patients older than 60 years.

Hepatic impairment

ATEROCON LA has not been studied in patients with hepatic impairment. Caution should be exercised in these patients.

Renal impairment

ATEROCON LA has not been studied in patients with renal impairment. Caution should be exercised in these patients.

Paediatric population

ATEROCON LA should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Method of administration

General recommendations

Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

ATEROCON LA is for oral use, should be taken once daily in the morning.

ATEROCON LA modified-release hard capsules may be administered with or without food. They may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of food. The granules must be swallowed whole and not chewed or crushed.
ATEROCON LA modified-release hard capsules and/or their contents should not be crushed or chewed.

Administration by sprinkling capsule contents on food
The capsules may be carefully opened, and the beads sprinkled over soft food.
The food should not be warm because this could affect the modified-release properties of this formulation.
The mixture of medicine and food should be consumed immediately in its entirety. This soft food mixture should not be chewed but swallowed only.
The medicine and food mixture should not be stored for future use.

ATEROCON LA, administered as a single dose, provides comparable overall exposure (AUC) of methylphenidate compared to the same total dose of Immediate Release methylphenidate administered twice daily.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Anxiety, tension and agitation (see section 4.4)
- Family history or diagnosis of Tourette's syndrome (see section 4.4)
- Hyperthyroidism

- Glaucoma
- Phaeochromocytoma
- Pre-existing cardiovascular disorders including hypertension, heart failure, arterial occlusive disease, angina pectoris, 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 (see section 4.4)
- During treatment with monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those medicines, due to risk of hypertensive crisis (see section 4.5)
- Pregnancy and lactation (see section 4.6)
- 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) (see section 4.5)
- Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke.

4.4 Special warnings and precautions for use

General

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

Treatment with ATEROCON LA is not indicated in all cases of Attention-deficit/Hyperactivity disorder, and should be considered only after detailed history-taking and evaluation. The decision to prescribe ATEROCON LA should depend on an assessment of the severity of symptoms and, in paediatric patients, their appropriateness to the child's age and not simply on the presence of one or more abnormal behavioural characteristics.

ATEROCON LA should not be used for the treatment of attention-deficit or hyperactivity secondary to amenable causes, including acute stress reactions.

Chronic abuse of ATEROCON LA can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes may occur. Abuse of ATEROCON LA may prove a problem in predisposed patients e.g. in emotionally unstable individuals or those with a history of drug dependence or alcoholism.

ATEROCON LA should therefore be used only under medical supervision. Clinical data indicate that children given ATEROCON LA are not more likely to abuse drugs than adolescents or adults.

Cardiovascular

Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Sudden death has been reported in association with the use of methylphenidate at usual doses in patients with pre-existing structural cardiac abnormalities or other serious heart problems. A causal relationship with ATEROCON LA has not been established since some of these conditions alone may carry an increased risk of sudden death. ATEROCON LA generally should not be used in patients with known structural cardiac abnormalities or other serious cardiac disorders that may increase the risk of sudden death due to its sympathomimetic effects. Before initiating ATEROCON LA treatment, patients should be assessed for pre-existing cardiovascular disorders such as a congenital long QT syndrome, or a family history of sudden death and ventricular dysrhythmia (see section 4.2).

Misuse and Cardiovascular Events

Misuse of ATEROCON LA, may be associated with sudden death and other serious cardiovascular adverse events.

Cardiovascular conditions

ATEROCON LA is contraindicated in patients with hypertension. ATEROCON LA increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension and severe cardiovascular disorders (see section 4.3).

Blood pressure should be monitored at appropriate intervals in all patients taking ATEROCON LA. Patients who develop symptoms suggestive of cardiac disease during ATEROCON LA treatment should undergo a prompt cardiac evaluation.

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Cerebrovascular conditions

Patients with pre-existing central nervous system (CNS) abnormalities, e.g. cerebral aneurysm and/or other vascular abnormalities such as vasculitis or pre-existing stroke should not be treated with ATEROCON LA.

Patients with additional risk factors (history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed regularly for neurological/psychiatric signs and symptoms after initiating treatment with ATEROCON LA (see above paragraph on Cardiovascular Conditions and section 4.5).

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing ATEROCON LA. Prior to initiating treatment with ATEROCON LA, patients should be assessed for pre-existing psychiatric disorders and a family history of psychiatric disorders (see sections 4.1 and 4.2). Treatment of ADHD with ATEROCON LA should not be initiated in patients with acute psychosis, acute mania or acute suicidality. These acute conditions should be treated and controlled before ADHD treatment is considered.

In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric symptoms, ATEROCON LA should not be given to patients unless the benefit outweighs the potential risk.

Psychotic symptoms

Psychotic symptoms, including visual and tactile hallucinations or mania have been reported in patients administered recommended therapeutic doses of ATEROCON LA (see section 4.8). Medical practitioners should consider treatment discontinuation.

Aggressive behaviour

Emergent aggressive behaviour or an exacerbation of baseline aggressive behaviour has been reported during methylphenidate as in ATEROCON LA therapy. However, patients with ADHD may experience aggression as part of their medical condition. Therefore, a causal association with treatment may be difficult to assess. Medical practitioners should evaluate the need for adjustment of treatment regimen in patients experiencing these behavioural changes, bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered.

Suicidal tendency

Patients with emergent suicidal ideation and behaviour during treatment for ADHD should be evaluated immediately by their medical practitioner. The medical practitioner should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Tics

ATEROCON LA is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported (see section 4.8). Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in patients should precede use of ATEROCON LA for ADHD treatment. ATEROCON LA is contraindicated in case of diagnosis or family history of Tourette's syndrome (see section 4.3). Patients should be regularly monitored for the emergence or worsening of tics during treatment with ATEROCON LA.

Serotonin syndrome

Serotonin syndrome has been reported following co-administration of methylphenidate with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The concomitant use of ATEROCON LA and serotonergic medicines is not recommended as this may lead to the development of serotonin syndrome. The symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g. tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g. tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Prompt recognition of these symptoms is important so that treatment with ATEROCON LA and serotonergic medicines can be immediately discontinued, and appropriate treatment instituted (see section 4.5).

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both paediatric and adult patients. Priapism generally developed after some time on the medicine, often subsequent to an increase in dose. Priapism has also been reported during a period of medicine withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Growth retardation

Reduced weight gain and slight growth retardation have been reported with the long-term use of methylphenidate (see section 4.8). Growth and weight should be monitored during treatment with ATEROCON LA, and patients who are not growing or gaining height or weight as expected or are losing weight may need to have their treatment interrupted and adjusted.

Haematological effects

The long-term safety and efficacy profiles of ATEROCON LA are not fully known. Patients requiring long-term therapy should therefore be carefully monitored and complete and differential blood counts and a platelet count performed periodically. In the event of haematological disorders appropriate medical intervention should be considered (see section 4.8).

Seizures

ATEROCON LA should be used with caution in patients with epilepsy as clinical experience has shown that it can cause an increase in seizure frequency. If seizure frequency increases, ATEROCON LA should be discontinued.

Drug abuse and dependence

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

Caution is called for in emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because they may increase the dosage on their own initiative.

Withdrawal

Careful supervision is required during ATEROCON LA withdrawal since this may unmask depression as well as the effects of chronic overactivity. Some patients may require long-term follow-up.

Paediatric population

ATEROCON LA is not indicated in children less than six years of age.

Treatment with ATEROCON LA is not indicated in all cases of Attention-Deficit/Hyperactivity disorder and should be considered only after detailed history-taking and evaluation. The decision to prescribe ATEROCON LA should depend on the medical practitioner assessment of the chronicity and severity of the child's symptoms and, their appropriateness to the child's age. Prescription should not depend solely on the presence of one or more abnormal behavioural characteristics. Where these symptoms are associated with acute stress reactions, treatment with ATEROCON LA is not indicated.

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4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

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

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

Reported data indicated that methylphenidate coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital (phenobarbitone), phenytoin, primodone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dose of these medicines already being taken and establish plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

Anti-hypertensive medicines

Methylphenidate 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 methylphenidate with any other active substances that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in section 4.4).

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

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive medicines, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment. In case of very high alcohol concentrations the kinetic profile may change towards a more immediate-release-like pattern.

Use with serotonergic medicines

There have been reports of serotonin syndrome following co-administration of methylphenidate with serotonergic medicines. If concomitant use of methylphenidate with a serotonergic medicine is warranted, prompt recognition of the symptoms of serotonin syndrome is important (see section 4.4). ATEROCON LA 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, methylphenidate treatment should not be used on the day of surgery.

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Use with centrally acting alpha-2 agonists (e.g. clonidine or dexmedetomidine)

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

Serious adverse events including sudden death may occur in concomitant use with clonidine or dexmedetomidine, although no causality for the combination has been established.

Use with dopaminergic medicines

Caution is recommended when administering methylphenidate with dopaminergic substances, including antipsychotics.

Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

Medicine/Laboratory test

ATEROCON LA may induce false positive laboratory tests for amphetamines, particularly with immunoassays screen test.

Antacids or acid suppressants

ATEROCON LA should not been taken together with with H2 receptor blockers, proton pump inhibitors or antacids, as this could lead to a faster release of the total amount of methylphenidate.

Since the modified-release characteristics of ATEROCON LA are pH dependent, the co-administration of antacids or acid suppressants could alter the release of methylphenidate.

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4.6 Fertility, pregnancy and lactation

Pregnancy

ATEROCON LA is contraindicated in pregnancy as safety has not been demonstrated

(see section 4.3).

Breastfeeding

Methylphenidate has been found in the breastmilk of a woman treated with

methylphenidate.

Mothers on ATEROCON LA should not breastfeed their infants.

Fertility

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

4.7 Effects on ability to drive and use machines

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision, (see section 4.8). Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with methylphenidate. If the ADRs with methylphenidate prolonged-release and the other methylphenidate formulations frequencies were different, the highest frequency of both databases was used.

Frequency estimate:

Frequent (≥ 1/100)

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Less frequent (< 1/100)

Not known (cannot be estimated from the available data).

System organ class	**Adverse Drug Reaction Frequency**		
	Frequent	**Less frequent**	**Not known**
Infections and infestations	Nasopharyngitis, upper respiratory tract infection[#], sinusitis[#]	Gastroenteritis	
Blood and lymphatic system disorders		Anaemia[†], leucopenia[†], thrombocytopenia, thrombocytopenic purpura	Pancytopenia
Immune system disorders		Hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritus, rashes and eruptions	
Metabolism and nutrition disorders*	Anorexia, decreased appetite[†],		

	moderately reduced weight and height gain during prolonged use in children*		
Psychiatric disorders*	Insomnia, nervousness, affect lability, aggression*, agitation*, anxiety*†, depression*#, irritability, abnormal behaviour*, mood swings, tics*, initial insomnia#, depressed mood#, libido decreased#, tension#, bruxism#, panic attack#	Psychotic disorders*, auditory, visual and tactile hallucination*, anger, suicidal ideation*, mood altered, restlessness†, tearfulness, worsening of pre-existing tics of Tourette's syndrome*, logorrhoea, hypervigilance, sleep disorder, mania*†, disorientation, libido disorder, confusional state†, suicidal attempt (including completed suicide)*†,	Delusions*†, thought disturbances*, confusional state, dependence [cases of abuse and dependence have been described, more often with immediate release formulations]

		transient depressed mood*, abnormal thinking, apathy†, repetitive behaviours, over-focussing	
Nervous system disorders	Headache, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, paraesthesia#, tension headache#	Sedation, tremor†, lethargy#, akathisia#, convulsions, choreoathetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS: reports were poorly documented, and, in most cases, patients were also receiving other medicines, so the role of methylphenidate is unclear)	Cerebrovascular disorders*† (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsion*, migraine†, dysphemia
Eye disorders	Accommodation disorder#	Blurred vision†, dry eye#,	Mydriasis, ocular hypertension

		difficulties in visual accommodation, visual impairment diplopia	
Ear and labyrinth disorders	Vertigo[#]		Tinnitus[#]
Cardiac disorders*	Dysrhythmia, tachycardia, palpitations	Chest pain angina pectoris cardiac arrest myocardial infarction	Supraventricular tachycardia, bradycardia, ventricular extrasystoles[†], extrasystoles[†], cardiac discomfort[#]
Vascular disorders*	Hypertension	Hot flush[#], cerebral arteritis and/or occlusion, peripheral coldness[†], Raynaud's phenomenon	Flushing[#]
Respiratory, thoracic and mediastinal disorders	Cough, oropharyngo-laryngeal pain,	Dyspnoea[†]	Epistaxis[#]
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, nausea[†],	Constipation[†]	Retching[#]

	abdominal discomfort, vomiting, dry mouth†, dyspepsia#		
Hepatobiliary disorders	Alanine aminotransferase increased#	Hepatic enzyme increased, abnormal liver function, including acute hepatic failure and hepatic coma, blood alkaline phosphatase increased, blood bilirubin increased†	
Skin and subcutaneous tissue disorders	Hyperhidrosis†, alopecia, pruritis, rash, urticaria	Angioneurotic oedema, bullous conditions, exfoliative conditions, macular rash erythema, erythema multiforme, exfoliative dermatitis, fixed drug eruption	Dry skin

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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, menstruation disorder[#], impairment of libido[#]	Priapism, erection increased* and prolonged erection*, breast pain[#]
General disorders and administration site conditions	Pyrexia, growth retardation during prolonged use in children*, fatigue[†], irritability[#], feeling jittery*, asthenia[#], thirst[#]	Sudden cardiac death*	Hyperpyrexia, disturbance in attention[#]' influenza like illness[#]
Investigations	Changes in blood pressure and heart rate (usually an increase)*,	Cardiac murmur*, platelet count decreased, increased hepatic enzyme,	Blood thyroid stimulating hormone increased[#]

	weight decreased*	increased blood alkaline phosphatase, increased blood bilirubin, abnormal white blood cell count	
Social circumstances			Partner stress#, family stress#

*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 children and adolescents.

^ 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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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, such as ATEROCON LA.

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, and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdose.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine should be given.

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

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

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class:

A.1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Psychoanaleptics, psychostimulants, agents used for ADHD and nootropics; centrally acting sympathomimetics

ATC Code: N06BA04

Mechanism of action

Methylphenidate is a racemate, consisting of a 1:1 mixture of d-methylphenidate and l-methylphenidate.

Methylphenidate is a central nervous system stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood, but its stimulant effects are thought to be due to inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine. The mechanism by which methylphenidate exerts its mental and behavioural effects in children is not clearly established, nor is there conclusive evidence showing how these effects relate to the condition of the central nervous system.

The effect of treatment with 40 mg dexmethylphenidate hydrochloride, the pharmacologically active d-enantiomer of methylphenidate, on QT/QTc interval was evaluated in a study in 75 healthy adult volunteers. The maximum mean prolongation of QTcF intervals was < 5 millisecond (ms), and the upper limit of the 90 % confidence interval was below 10 ms for all time matched comparisons versus placebo. This was

below the threshold of clinical concern and no exposure response relationship was evident.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of methylphenidate hydrochloride (modified-release capsules) to children diagnosed with ADHD and adults, methylphenidate plasma concentration-time profiles show a bi-modal profile (i.e. two distinct peaks approximately four hours apart). The fluctuations between peak and trough plasma methylphenidate concentrations are smaller for methylphenidate (modified-release capsules) given once a day compared to methylphenidate (immediate-release) tablets given twice a day.

Food effects

ATEROCON LA modified-release hard capsules may be administered with or without food. There were no differences in the bioavailability of modified-release methylphenidate when administered with either a high fat breakfast or apple sauce compared to administration in the fasting conditions. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the modified-release hard capsule, the contents may be sprinkled on soft food and administered immediately (see section 4.2).

Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Distribution

In the blood, methylphenidate and its metabolites are distributed in the plasma (57 %) and in the erythrocytes (43 %). Methylphenidate and its metabolites have a low plasma protein-binding (10 to 33 %).

The apparent distribution volume has been calculated as 13,1 L/kg after an oral dose; the volume of distribution after intravenous dose (Vss) is 2,23 L/kg for the racemate in healthy adult volunteers. The volume of distribution was 2,65 ± 1,11 L/kg for dextromethylphenidate (d-MPH) and 1,80 ± 0,91 L/kg for levomethylphenidate (l-MPH).

Methylphenidate is excreted in breast milk.

Biotransformation

Peak plasma concentrations of PPAA (ritalinic acid) are attained approximately 2 hours after administration of methylphenidate and are 30 to 50 times higher than those of the unchanged substance. The half-life of PPAA is roughly twice as long as that of methylphenidate, and the mean systemic clearance is 0,17 L/h/kg.

Elimination

Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours. The systemic clearance is 0,40 ± 0,12 L/h/kg for d-MPH and 0,73 ± 0,28 L/h/kg for l-MPH. After oral administration, 78 – 97 % of the dose administered is excreted in the urine and 1 – 3 % in the faeces in the form of metabolites within 48 to 96 hours. Only small quantities (< 1 %) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as α-phenyl-2 piperidine acetic acid (60 – 86 %), probably pH independent.

Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Characteristics in patients

There are no apparent differences in the pharmacokinetic of methylphenidate between children with hyperkinetic disorders/ADHD and healthy adult volunteers. Elimination data from patients with normal renal function suggest that renal excretion of unchanged methylphenidate would hardly be diminished in the presence of impaired renal function. However, renal excretion of the main metabolite α-phenyl-2-piperidine acetic acid may be reduced.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Ethylcellulose

Hydroxypropylcellulose

Hypromellose

Methacrylic acid-methyl methacrylate copolymer (1:1)

Microcrystallíne cellulose

Talc

Triethyl citrate

Capsule shell

Gelatin

Titanium dioxide (E171)

Additionally, in ATEROCON LA 10 mg modified-release hard capsules, ATEROCON LA 30 mg modified-release hard capsules, ATEROCON LA 40 mg modified-release hard capsules and ATEROCON LA 60 mg modified-release hard capsules:

Iron oxide yellow (E172)

Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Printed ink

Iron oxide black (E172)

Propylene glycol

Shellac glaze

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicine must be stored at or below 25 ºC in original container.

Keep container tightly closed to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with child-resistant closure (PP)

28, 30, 56, 60, 84, 100 modified-release hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Austell Pharmaceuticals (Pty) Ltd, 540431-5, Aterocon LA, Modified-release hard gelatin capsules, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

www.austell.co.za

8. REGISTRATION NUMBERS

ATEROCON LA 10 mg modified-release hard capsules: 54/1.2/0431

ATEROCON LA 20 mg modified-release hard capsules: 54/1.2/0432

ATEROCON LA 30 mg modified-release hard capsules: 54/1.2/0433

ATEROCON LA 40 mg modified-release hard capsules: 54/1.2/0434

ATEROCON LA 60 mg modified-release hard capsules: 54/1.2/0435

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 May 2023

10. DATE OF REVISION OF THE TEXT