PROFESSIONAL INFORMATION

ATTENCIT RANGE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ATTENCIT 10 mg, hard gelatine capsule

ATTENCIT 18 mg, hard gelatine capsule

ATTENCIT 25 mg, hard gelatine capsule

ATTENCIT 40 mg, hard gelatine capsule

ATTENCIT 60 mg, hard gelatine capsule

ATTENCIT 80 mg, hard gelatine capsule

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

ATTENCIT (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).

Anyone considering the use of ATTENCIT in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behaviour. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behaviour), clinical worsening, or unusual changes in behaviour.

Families and caregivers should be advised of the need for close observation and communication with the prescriber. ATTENCIT is approved for ADHD in paediatric and adult patients. ATTENCIT is not approved for major depressive disorder.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains atomoxetine hydrochloride equivalent to either 10 mg, 18 mg, 25 mg, 40 mg, 60 mg or 80 mg atomoxetine.

ATTENCIT capsules are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules.

10 mg, capsule size 4, white opaque cap and body imprinted with A910 on both cap and body in black ink.

18 mg, capsule size 3, gold opaque cap and white opaque body imprinted with A918 on both cap and body in black ink.

25 mg, capsule size 3, blue opaque cap and white opaque body imprinted with A925 on both cap and body in black ink.

40 mg, capsule size 2, blue opaque cap and body imprinted with A940 on both cap and body in black ink.

60 mg, capsule size 2, blue opaque cap and gold opaque body imprinted with A960 on both cap and body in black ink.

80 mg, capsule size 1, brown opaque cap and white opaque body imprinted with A980 on both cap and body in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ATTENCIT is indicated for the treatment of Attention-Deficit / Hyperactivity Disorder (ADHD) in children 6 years of age or older, adolescents and adults.

4.2 Posology and method of administration

Treatment must be initiated by or under the supervision of medical practitioner with appropriate knowledge and experience of childhood and/or adolescent behavioural disorders (for example, paediatrician or child/adolescent psychiatrist).

Posology

The recommended initial dose and subsequent dosage escalations of ATTENCIT should not be exceeded because of potential side effects (see section 4.8).

Dosing of children and adolescents up to 70 kg body weight:

ATTENCIT should be initiated at a total daily dose of approximately 0,5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1,2 mg/kg/day (depending on the patient's weight and available dosage strengths of ATTENCIT). No additional benefit has been demonstrated for doses higher than 1,2 mg/kg/day.

Dosing of children and adolescents over 70 kg body weight and adults:

ATTENCIT should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg. The maximum recommended total daily dose for adults is 80 mg.

Special populations

Hepatic insufficiency

Use of ATTENCIT in patients with impairment of liver function is contraindicated (see section 4.3).

Renal insufficiency

Subjects with end-stage renal disease had higher systemic exposure to atomoxetine than healthy subjects, but there was no difference when exposure was corrected for mg/kg dose. ATTENCIT can therefore be administered to ADHD patients with end-stage renal disease or lesser degrees of renal insufficiency using the usual dosing regimen. Cautious titration of ATTENCIT to the desired clinical response is recommended. ATTENCIT may exacerbate hypertension in patients with end-stage renal disease.

CYP2D6 poor metabolisers

Patients with this genotype have a several-fold higher exposure to atomoxetine when compared to patients with a functional enzyme. Poor metabolisers are therefore at higher risk of adverse events (see section 5.2).

For patients with a known poor metaboliser genotype, a lower starting dose and slower up titration of the dose may be considered.

Elderly population

The use of atomoxetine in patients over 65 years of age has not been systematically evaluated.

Paediatric population under six years of age

The safety and efficacy of ATTENCIT in children under 6 years of age have not been established. Therefore, ATTENCIT should not be used in children under 6 years of age (see section 4.4).

Method of administration

ATTENCIT may be taken with or without food.

ATTENCIT may be discontinued without tapering the dose.

ATTENCIT capsules are not intended to be opened (see section 4.4). ATTENCIT is an ocular irritant. In the event of capsule content coming into contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Long-term use:

No fixed dose-response studies have been conducted in adults. The recommended daily dose of 80 mg reflects the optimal daily dose of 1,2 mg/kg/day in children and adolescents.

No controlled long-term studies have been conducted in adults. Open-label study data from 384 patients with up to 97 weeks of treatment are consistent with maintenance of efficacy in long-term treatment.

Missing a dose:

If patients miss a dose, they should take it as soon as possible; however, they should not take more than the prescribed total daily amount of ATTENCIT in any 24 hours period.

4.3 Contraindications

- Hypersensitivity to atomoxetine or to any of the ingredients of ATTENCIT.
- ATTENCIT should not be used in patients with uncontrolled hypertension, or impairment of liver function.
- ATTENCIT should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important (for example 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate) (see section 4.4), or cerebrovascular disorders.
- ATTENCIT should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see section 4.4).
- ATTENCIT should be permanently discontinued in patients with jaundice or markedly increased liver enzyme values (see section 4.4).
- ATTENCIT should not be used in patients with narrow angle glaucoma, due to an increased risk of mydriasis.
- ATTENCIT should not be used in combination with monoamine oxidase inhibitors (MAOIs), including linezolid. ATTENCIT should not be used within a minimum of 2 weeks after discontinuing therapy with MAOIs. Treatment with MAOIs should not be initiated within 2 weeks after discontinuing ATTENCIT.

4.4 Special warnings and precautions for use

Suicide-related behaviour:

Treatment must only be initiated by or under the supervision of a medical practitioner with appropriate knowledge and experience of childhood and adolescent behaviour disorders (e.g. paediatrician or child/adolescent psychiatrist).

Suicidal behaviour, suicidal ideation, hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability is more frequently observed among children and adolescents treated with atomoxetine. Patients beginning treatment for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour, hostility and emotional lability. The possibility of rare, serious psychiatric adverse effects cannot be excluded.

There is some evidence that the risk of psychiatric adverse events is increased in children with a personal history of mood disorders, or who have a family history of mood disorders.

Treatment must only be initiated by or under the supervision of a medical practitioner with appropriate knowledge and experience of childhood and adolescent behaviour disorders (e.g. paediatrician or child/adolescent psychiatrist).

Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour. Patients or caregivers should be advised to immediately report any symptoms of depression and/or suicidal ideation.

Sudden death and pre-existing cardiac abnormalities:

Sudden death has occurred in patients with structural cardiac abnormalities taking atomoxetine as in ATTENCIT at the usual doses. Although some serious structural cardiac abnormalities alone carry an

increased risk of sudden death, ATTENCIT should be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

ATTENCIT is contraindicated in patients with severe cardiovascular disorders (see section 4.3).

Possible allergic events:

Allergic reactions including anaphylactic reactions, rash, angioedema and urticarial rash have been reported in patients taking ATTENCIT.

Cardiovascular effects:

ATTENCIT can significantly increase heart rate and blood pressure and therefore, both should be measured before and during treatment in order that possible clinically important increases be detected.

Many patients taking ATTENCIT experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg). However, studies indicate that approximately 5 to 10 % of children and adults experience clinically important changes in heart rate (20 beats per minute or greater) or blood pressure (15 to 20 mm Hg or greater). ATTENCIT should be used with caution in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease, and not be administered to patients with severe cardiovascular disorders whose condition would be expected to deteriorate should clinically significant changes in blood pressure or heart rate be experienced (see section 4.3).

In addition, ATTENCIT should be used with caution in patients with congenital QT syndrome, acquired long QT (for example, due to concomitant use with medicines that prolong the QT) or a family history of QT prolongation.

Orthostatic hypotension has also been reported, therefore, ATTENCIT should be used with caution in any condition that may predispose patients to hypotension, or conditions associated with abrupt heart rate or blood pressure changes.

Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during ATTENCIT treatment should undergo a prompt specialist cardiac evaluation.

ATTENCIT should not be used in patients with Raynaud's phenomenon.

Cerebrovascular effects:

Patients with additional risk factors for cerebrovascular conditions (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 ATTENCIT.

Hepatic effects:

ATTENCIT should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted (see section 4.3). Liver injury manifested by elevated hepatic enzymes and bilirubin with jaundice has been reported (associated with severe liver injury and acute liver failure in some cases). Signs and symptoms likely to indicate liver involvement include pruritus, dark urine, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms. Laboratory testing to determine liver enzyme levels and bilirubin should be done upon the first sign or symptom of possible liver involvement. Due to the seemingly idiosyncratic nature of the liver injury, routine monitoring of liver function is unlikely to be helpful in minimising the risk of such reactions.

Psychotic or manic symptoms:

Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, mania or agitation in patients without a prior history of psychotic illness or mania can be caused by ATTENCIT

at usual doses. If such symptoms occur, consideration should be given to a possible causal role of ATTENCIT, and discontinuation of treatment should be considered. The possibility that ATTENCIT will cause the exacerbation of pre-existing psychotic or manic symptoms cannot be excluded.

Seizures:

Seizures are a potential risk with ATTENCIT therapy and it should be used with caution in patients with a history of seizures. Treatment may need to be stopped in those who develop seizures or have an increase in seizure frequency (see section 4.5).

Depression:

ATTENCIT lacks efficacy as treatment modality in depression.

New-onset or worsening of Co-morbid Depression, Anxiety and Tics:

In a controlled study of paediatric patients with ADHD and co-morbid chronic motor tics or Tourette's Disorder, treated with ATTENCIT did not experience worsening of tics compared to placebo-treated patients.

Adolescent patients with ADHD and co-morbid Major Depressive Disorder, treated with ATTENCIT did not experience worsening of depression compared to placebo-treated patients.

Neither paediatric patients nor adult patients with ADHD and co-morbid anxiety disorders, when treated with ATTENCIT, experienced worsening of anxiety compared to placebo-treated patients.

There have been rare postmarketing reports of anxiety and depression or depressed mood and very rare reports of tics in patients taking ATTENCIT (see section 4.8).

Patients who are being treated for ADHD with ATTENCIT should be monitored for the appearance or worsening of anxiety symptoms, depressed mood and depression or tics.

Growth and development:

Weight gain and longitudinal growth should be monitored during treatment with ATTENCIT. Studies indicated a mean initial decrease in weight and height gain. It is recommended that growth be monitored and consideration given to dose reduction or interrupting treatment in patients who are not growing or gaining weight satisfactorily.

Effects on micturition:

Studies in adult ADHD patients indicate the rates of urinary retention and urinary hesitation were increased. Therefore, complaints of urinary retention or urinary hesitancy should be considered potentially related to ATTENCIT.

Geriatric use:

The safety and efficacy of ATTENCIT in geriatric patients have not been established.

Paediatric population:

The safety and efficacy of ATTENCIT in paediatric patients less than 6 years of age have not been established, and should therefore not be used. The efficacy of ATTENCIT beyond 18 months of treatment and safety of ATTENCIT beyond 2 years of treatment have not been systematically evaluated.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

ATTENCIT should not be used with MAOIs, including linezolid (see section 4.3).

CYP2D6 inhibitors (SSRIs (e.g., fluoxetine, paroxetine), quinidine, terbinafine):

In patients receiving these medicines, ATTENCIT exposure may be 6- to 8-fold increased and $C_{ss\ max}$ 3 to 4 times higher, because it is metabolised by the CYP2D6 pathway. Slower titration and final lower dosage of ATTENCIT may be necessary in patients who are already taking CYP2D6 inhibitor

medicines. If a CYP2D6 inhibitor is prescribed or discontinued after titration to the appropriate ATTENCIT dose has occurred, the clinical response and tolerability should be re-evaluated for that patient to determine if dose adjustment is needed.

Salbutamol or other beta-adrenergic receptor agonists:

ATTENCIT should be administered with caution to patients being treated with systemically administered (oral, inhaled or intravenous) salbutamol or other β-2 agonists, as cardiovascular effects can be potentiated.

Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either ATTENCIT or salbutamol (or other $beta_2$ agonists) in the event of significant increases in heart rate and blood pressure during co-administration of these medicines.

QT interval prolongation potential:

There is the potential for an increased risk of QT interval prolongation when ATTENCIT is administered with other QT prolonging medicines (such as neuroleptics, class IA and III anti-dysrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, or cisapride), medicines that cause electrolyte imbalance (such as thiazide diuretics), and medicines that inhibit CYP2D6 (see section 4.4).

Medicines with a potential to cause seizures:

Seizures are a potential risk with ATTENCIT. Caution is advised with concomitant use of medicines which are known to lower the seizure threshold (such as tricyclic antidepressants or SSRIs, neuroleptics, phenothiazines or butyrophenone, mefloquine, chloroquine, bupropion or tramadol) (see section 4.4). In addition, caution is advised when stopping concomitant treatment with benzodiazepines due to potential withdrawal seizures.

Pressor medicines (medicines that increase blood pressure):

Because of possible effects on blood pressure, ATTENCIT should be used cautiously with pressor agents or medicines that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either ATTENCIT or pressor medicines may be justified in the case of significant change in blood pressure.

Anti-hypertensive medicines:

ATTENCIT should be used cautiously with anti-hypertensive medicines. Because of a possible increase in blood pressure, ATTENCIT may decrease the effectiveness of anti-hypertensive medicines or medicines used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of ATTENCIT or anti-hypertensive medicines may be justified in the case of significant changes of blood pressure.

Cytochrome P450 enzyme:

ATTENCIT does not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6 and CYP2C9. ATTENCIT is principally metabolised by the CYP2D6 pathway. In CYP2D6 extensive metabolisers, inhibitors of CYP2D6 increase ATTENCIT steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metabolisers.

Co-administration of cytochrome P450 inhibitors to CYP2D6 poor metabolisers will not increase the plasma concentrations of ATTENCIT.

Slower titration of ATTENCIT may be necessary in those patients who are also taking CYP2D6 inhibitor medicines as the side effects are increased in frequency in patients who are poor CYP2D6 metabolisers (see section 4.8).

Methylphenidate:

Co-administration of methylphenidate with ATTENCIT does not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Medicines that affect gastric pH:

Medicines that elevate gastric pH (magnesium hydroxide / aluminium hydroxide, omeprazole) have no effect on ATTENCIT bioavailability.

Alcohol:

Consumption of ethanol with ATTENCIT does not change the intoxicating effects of ethanol.

Midazolam:

Co-administration of ATTENCIT (60 mg twice daily for 12 days) with midazolam, a model compound for CYP3A4 metabolised medicines (single dose of 5 mg), results in 15 % increase in AUC of midazolam.

However, no dose adjustment is recommended for medicines metabolised by CYP3A.

Medicines that affect norepinephrine (noradrenaline):

Medicines that affect norepinephrine (noradrenaline) should be used cautiously when co-administered with ATTENCIT because of the potential for additive or synergistic pharmacological effects. Examples include antidepressants, such as imipramine, venlafaxine, and mirtazapine, or the decongestants pseudoephedrine or phenylephrine.

Medicines highly bound to plasma protein:

ATTENCIT does not affect the binding of warfarin, aspirin, phenytoin or diazepam to human albumin *in vitro*. Similarly, these medicines will not affect the binding of ATTENCIT to human albumin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy have not been demonstrated in pregnancy.

Breastfeeding

Safety and efficacy have not been demonstrated during breastfeeding. Studies show that atomoxetine, as in ATTENCIT and/or it's metabolites were excreted in the milk of rats. It is not known if ATTENCIT is excreted in human milk. Women taking ATTENCIT should not breastfeed their infants.

4.7 Effects on ability to drive and use machines:

ATTENCIT has been associated with fatigue, somnolence and dizziness in paediatric and adult patients (see section 4.8). Patients should be advised to use caution when driving a vehicle or operating hazardous machinery until they are reasonably certain that their performance is not affected by ATTENCIT.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain and decreased appetite are the adverse events most frequently associated with ATTENCIT, but seldom lead to discontinuation of treatment. Abdominal pain and decreased appetite are usually transient.

Associated with decreased appetite, some patients experienced growth retardation early in therapy in terms of both weight and height gain. On average, after an initial decrease in weight and height gain, patients treated with ATTENCIT recovered to mean weight and height as predicted by group baseline data over the long-term treatment.

Nausea, vomiting and somnolence can occur, particularly during the first month of therapy. However, these episodes are usually mild to moderate in severity and transient, and do not result in a significant number of discontinuations from therapy.

Increases in heart rate, systolic and diastolic blood pressure have also been experienced in both adult and paediatric patients.

Because of its effect on noradrenergic tone, orthostatic hypotension and syncope have been reported in patients taking atomoxetine, as in ATTENCIT. ATTENCIT should be used with caution in any condition that may predispose patients to hypotension.

Tabulated list of adverse effects

Child and adolescent patients:

System Organ Class	Frequency	Side effects
Immune system disorders	Less frequent	Anaphylactic reactions, angioedema, rash, urticaria
Metabolism and nutrition disorders	Frequent	Anorexia, decreased appetite
Psychiatric disorders	Frequent	Aggression, hostility, irritability, mood swings, insomnia (initial, middle and terminal), agitation, anxiety, depression (including major), depressive symptoms, depressed mood, dysphoria
	Less frequent	Suicidal ideation, suicidal behaviour, anger, emotional lability, psychosis, hallucinations
	Frequency unknown	Mania, hypomania, delusional thinking, excoriation
Nervous system disorders	Frequent	Dizziness, headache, somnolence, sedation, paraesthesia

	Less frequent	Syncope, migraine, hypoesthesia, seizure, tremor, vasovagal syncope, tics
Eye disorders	Frequent Less frequent	Mydriasis Blurred vision, conjunctivitis
Cardiac disorders	Less frequent Frequency unknown	Palpitations, sinus tachycardia, QT interval prolongation Myocardial infarction
Vascular disorders	Frequency unknown	Peripheral vascular instability and/or Raynaud's phenomenon, potential to exacerbate pre-existing Raynaud's phenomenon, stroke
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, sinusitis, rhinorrhoea, cough
Gastrointestinal disorders	Frequent	Abdominal pain, upper abdominal pain, stomach discomfort, abdominal discomfort, epigastric discomfort, constipation, dyspepsia, nausea, vomiting
Hepatobiliary disorders	Less frequent	Increased blood bilirubin, abnormal liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, dermatitis, rash Hyperhidrosis
Renal and urinary disorders	Less frequent	Urinary hesitation, urinary retention

Reproductive system and breast disorders	Less frequent	Priapism, male genital pain
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue, lethargy, chest pain, irritability Asthenia Sudden death
Investigations	Frequent	Increased heart rate, increased systolic and diastolic blood pressure, orthostatic hypotension, weight decreased

Adults:

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Anaphylactic reactions, angioedema, rash, urticaria
Metabolism and nutrition disorders	Frequent	Decreased appetite
Psychiatric disorders	Frequent Less frequent Frequency unknown	Libido decrease, sleep disorder, agitation, insomnia (initial, middle and terminal), early morning awakening Restlessness Aggression, hostility, suicidal ideation, anger, suicidal behaviour, emotional lability, psychosis, sensory disturbances, hallucinations, anxiety, depression, depressed mood, mania, hypomania, delusional thinking
Nervous system disorders	Frequent	Dizziness, headache, somnolence, sedation, dysgeusia, paraesthesia, tremor

	Less frequent	Syncope, migraine, hypoesthesia, seizure, tics
Eye disorders	Less frequent	Blurred vision
Cardiac disorders	Frequent Less frequent Frequency unknown	Palpitations, tachycardia QT interval prolongation Myocardial infarction
Vascular disorders	Frequent Less frequent Frequency unknown	Flushing, hot flushes Peripheral coldness Peripheral vascular instability and/or Raynaud's phenomenon, potential to exacerbate pre-existing Raynaud's phenomenon, stroke
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Dyspnoea Sinusitis, rhinorrhoea, cough
Gastrointestinal disorders	Frequent	Abdominal pain, upper abdominal pain, stomach discomfort, abdominal discomfort, epigastric discomfort, dyspepsia, dry mouth, nausea, vomiting, constipation, flatulence
Hepatobiliary disorders	Less frequent	Increased blood bilirubin, abnormal liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Dermatitis, rash, hyperhidrosis Pruritus, allergic reactions, urticaria
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle spasms

Renal and urinary disorders	Frequent Less frequent	Dysuria, urinary hesitation, urine flow decreased, urinary retention, pollakiuria Micturition urgency
Reproductive system and breast disorders	Frequent Less frequent	Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, testicular pain Ejaculation failure, menstruation disorder, abnormal orgasm, priapism, irregular menstruation
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Fatigue, lethargy, chills, feeling jittery, irritability, thirst, asthenia Feeling cold, chest pain Sudden death
Investigations	Frequent	Decreased weight, increased heart rate and blood pressure

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 Reaction Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

There is limited clinical trial experience with ATTENCIT overdose.

Signs and symptoms:

The most commonly reported symptoms accompanying acute and chronic overdoses are somnolence, seizures, dizziness, tremor, abnormal behaviour and gastrointestinal symptoms. Hyperactivity and

agitation have also been reported. Most events were mild to moderate. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g. mydriasis, tachycardia, blood pressure increased, dry mouth) were also observed.

In some cases of overdose involving ATTENCIT, seizures and very rarely QT prolongation have been reported. There have also been reports of fatal, acute overdoses involving a mixed ingestion of ATTENCIT and at least one other medicine.

Management of overdose:

An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures.

Activated charcoal may be useful in limiting absorption if the patient presents within 1 hour of ingestion. Because ATTENCIT is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, centrally acting sympathomimetics

ATC code: N06BA09

Mechanism of action

Atomoxetine is a selective inhibitor and potent inhibitor of the presynaptic norepinephrine transporter, its presumed mechanism of action, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine has two major oxidative metabolites: 4-hydroxyatomoxetine and N-desmethylatomoxetine. 4-hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the noradrenaline transporter but, unlike atomoxetine, this metabolite also exerts some inhibitory activity at the serotonin transporter. However, any effect on this transporter is likely to be minimal, as the majority of 4-hydroxyatomoxetine is further metabolised such that it circulates in plasma at much lower

concentrations (1 % of atomoxetine concentration in extensive metabolisers and 0,1 % of atomoxetine concentration in poor metabolisers). N-desmethylatomoxetine has substantially less pharmacological activity compared with atomoxetine. It circulates in plasma at lower concentrations in extensive metabolisers and at comparable concentrations to the parent medicine in poor metabolisers at steady-state.

Atomoxetine is not a psychostimulant and is not an amphetamine derivative. In a randomised, double-blind, placebo-controlled, abuse-potential study in adults, comparing effects of atomoxetine and placebo, atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.

5.2 Pharmacokinetic properties

The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Absorption:

Atomoxetine is well absorbed after oral administration reaching mean maximal observed plasma concentration (C_{max}) approximately 1 to 2 hours after dosing and can be administered with or without food.

Distribution:

Atomoxetine is widely distributed and is extensively bound to plasma proteins, primarily albumin.

Biotransformation:

Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway.

The major oxidative metabolite formed is 4-hydroxyatomoxetine that is rapidly glucuronidated.

4-Hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations.

Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine can be formed by several other cytochrome P450 enzymes, but at a slower rate.

Atomoxetine does not inhibit or induce the CYP2D6 pathway.

Elimination:

The mean elimination half-life of atomoxetine after oral administration is 3,6 hours in extensive metabolisers and 21 hours in poor metabolisers. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine.

Linearity/non-linearity:

Pharmacokinetics of atomoxetine are linear over the range of doses studied in both extensive and poor metabolisers.

Pharmacokinetics in special patient groups

Hepatic impairment:

Hepatic impairment results in a reduced atomoxetine clearance, increased atomoxetine exposure (AUC increased 2-fold in moderate impairment and 4-fold in severe impairment), and a prolonged half-life of parent drug compared to healthy controls with the same CYP2D6 extensive metaboliser genotype (see section 4.2).

Renal impairment:

Atomoxetine mean plasma concentrations for end-stage renal disease (ESRD) subjects were generally higher than the mean for healthy control subjects shown by C_{max} (7 % difference) and $AUC_{0-\infty}$ (about 65 % difference) increases. After adjustment for body weight, the differences between the two groups are

minimised. Pharmacokinetics of atomoxetine and its metabolites in individuals with ESRD suggest that no dose adjustment would be necessary (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch

Dimethicone

Hard gelatine capsule

Pregelatinised starch

Sodium starch glycolate

Composition of hard gelatine capsules:

Gelatine

Titanium dioxide (E171)

Yellow iron oxide (E172)

Indigotine – FD&C Blue 2 (E132)

Black iron oxide (E172)

Red iron oxide (E172)

Black printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C in original blister packs or HDPE containers.

6.5 Nature and contents of container

ATTENCIT capsules are packed in opaque PVC/PVdC/PVC/aluminium blister packs of 10 or 14 then placed in an outer carton. Each carton contains 28 or 30 capsules.

ATTENCIT capsules are packaged in high density polyethylene (HDPE) containers with polypropylene closures. Bottles contain either 28, 30, 100 or 250 capsules.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

ATTENCIT 10 mg: A51/1.2/0376

ATTENCIT 18 mg: A51/1.2/0377

ATTENCIT 25 mg: A51/1.2/0378

ATTENCIT 40 mg: A51/1.2/0379

ATTENCIT 60 mg: A51/1.2/0380

ATTENCIT 80 mg: A51/1.2/0381

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

October 2020

10. DATE OF REVISION OF THE TEXT

October 2020