Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product name: ATTENTRA 10, 18, 25, 40, 60 & 80** **Dosage form & strength:** Capsules Atomoxetine hydrochloride equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg & 80 mg atomoxetine.
Date of Registration: 11.08.2020	**SAHPRA approval date: 9.07.2025**

PROFESSIONAL INFORMATION

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SCHEDULING STATUS:

S5

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

ATTENTRA (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 ATTENTRA 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 medical practitioner. ATTENTRA is approved for ADHD in paediatric and adult patients. ATTENTRA is not approved for major depressive disorder.

1. NAME OF THE MEDICINE:

ATTENTRA 10, each capsule contains atomoxetine 10 mg (as atomoxetine HCl).

ATTENTRA 18, each capsule contains atomoxetine 18 mg (as atomoxetine HCl).

ATTENTRA 25, each capsule contains atomoxetine 25 mg (as atomoxetine HCl).

ATTENTRA 40, each capsule contains atomoxetine 40 mg (as atomoxetine HCl).

ATTENTRA 60, each capsule contains atomoxetine 60 mg (as atomoxetine HCl).

ATTENTRA 80, each capsule contains atomoxetine 80 mg (as atomoxetine HCl).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

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

Sugar free.

3. PHARMACEUTICAL FORM:

Capsules

ATTENTRA 10: size 4 capsules, white opaque cap and body imprinted with ‘A910’ on both cap and body in black ink.

ATTENTRA 18: size 3 capsules, gold opaque cap and white opaque body imprinted with ‘A918’ on both cap and body in black ink.

ATTENTRA 25: size 3 capsules, blue opaque cap and white opaque body imprinted with ‘A925’ on both cap and body in black ink.

ATTENTRA 40: size 2 capsules, blue opaque cap and body imprinted with ‘A940’ on both cap and body in black ink.

ATTENTRA 60: size 2 capsules, blue opaque cap and gold opaque body imprinted with ‘A960’ on both cap and body in black ink.

ATTENTRA 80: size 1 capsules, 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:

ATTENTRA 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 a medical practitioner with appropriate knowledge and experience of childhood and/or adolescent behavioural disorders (for example,

paediatrician or child/adolescent psychiatrist) (see **section 4.4**).

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

ATTENTRA capsules are not intended to be opened. ATTENTRA 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.

Posology:

ATTENTRA may be discontinued without tapering the dose.

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

ATTENTRA 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 ATTENTRA). 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:

ATTENTRA 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.

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 demonstrated in children and adolescents.

No controlled long-term studies have been conducted in adults. Open-label study data up to 97 weeks of treatment with atomoxetine 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 ATTENTRA in any 24-hour period.

Special populations:

Renal and hepatic insufficiency:

For those ADHD patients who have hepatic insufficiency or end-stage renal disease, cautious titration of ATTENTRA to the desired clinical response is recommended (see **section 5.2**). ATTENTRA clearance may be reduced in patients with hepatic insufficiency. ATTENTRA may exacerbate hypertension in patients with end-stage renal disease.

Elderly population:

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

Paediatric population under six years of age:

The safety and efficacy of ATTENTRA in children under 6 years of age have not been established.

Therefore, ATTENTRA should not be used in children under 6 years of age (see **section 4.4**).

Method of administration:

For oral use. ATTENTRA may be taken with or without food.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in **section 6.1**.
- Monoamine oxidase inhibitors: ATTENTRA should not be used in combination with monoamine oxidase

inhibitors (MAOIs), including linezolid.

- ATTENTRA 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 atomoxetine (see **section 4.5**).
- Narrow angle glaucoma: ATTENTRA should not be used in patients with narrow-angle glaucoma, as the use of atomoxetine is associated with an increased incidence of mydriasis.
- Severe cardiovascular or cerebrovascular disorders: ATTENTRA should not be used in patients with severe cardiovascular or cerebrovascular disorders (see **section 4.4**). Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). Severe cerebrovascular disorders may include cerebral aneurysm or stroke.
- Pheochromocytoma: ATTENTRA should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see **section 4.4**).
- ATTENTRA should not be used in patients with impairment of liver function.

4.4 Special warnings and precautions for use:

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).

Suicide-related behaviour:

Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with ATTENTRA. In clinical trials, suicide-related behaviours were less frequent, but more frequently observed among children and adolescents treated with ATTENTRA compared to those treated with placebo, where there were no events. In adult clinical trials, there was no difference in the frequency of suicide-related behaviour between atomoxetine and placebo. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour.

Sudden death and pre-existing cardiac abnormalities:

Sudden death has been reported in patients with structural cardiac abnormalities who were taking ATTENTRA at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, ATTENTRA should only be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

Cardiovascular effects:

ATTENTRA can affect heart rate and blood pressure. Most patients taking ATTENTRA experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see **section 4.8**).

Long-term sustained changes in blood pressure may potentially contribute to clinical consequences such as myocardial hypertrophy.

As a result of these findings, patients who are being considered for treatment with ATTENTRA should have a careful history 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.

It is recommended that heart rate and blood pressure be measured and recorded before treatment is started and, during treatment, after each adjustment of dose and then at least every 6 months to detect possible clinically important increases. For paediatric patients the use of a centile chart is recommended. For adults, current reference guidelines for hypertension should be followed.

ATTENTRA should not be used in patients with severe cardiovascular or cerebrovascular disorders (see **section 4.3**). ATTENTRA should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure and heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

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

In addition, ATTENTRA should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation (see **sections 4.5** and **4.8**).

As orthostatic hypotension has also been reported, ATTENTRA 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.

Cerebrovascular effects:

Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease, concomitant medicines that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with ATTENTRA.

Hepatic effects:

Less frequently, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. Also, severe liver injury, including acute liver failure, have been reported. ATTENTRA should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.

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

Aggressive behaviour, hostility or emotional lability:

Hostility (predominantly aggression, oppositional behaviour and anger) was more frequently observed in clinical trials among children, adolescents and adults treated with ATTENTRA compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with ATTENTRA compared to those treated with placebo. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.

Severe cases have been reported concerning paediatric patients, including reports of physical assault, or threatening behaviour and thoughts of harming others. Families and caregivers of paediatric patients treated with ATTENTRA should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted, particularly after starting treatment or changing the dose. Physicians should evaluate the need for dose adjustment or treatment discontinuation in patients experiencing behavioural changes.

Possible allergic events:

Allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema and urticaria, have been reported in patients taking ATTENTRA.

Seizures:

Seizures are a potential risk with ATTENTRA. ATTENTRA should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified (see **section 4.5**).

Growth and development:

Growth and development should be monitored in children and adolescents during treatment with ATTENTRA. Patients requiring long‑term therapy should be monitored, and consideration should be given to dose reduction or interrupting therapy in children and adolescents who are not growing or gaining weight satisfactorily.

Clinical data do not suggest a deleterious effect of atomoxetine on cognition or sexual maturation; however, the amount of available long-term data is limited.

Patients requiring long-term therapy should be carefully monitored.

New-onset or worsening of comorbid depression, anxiety and tics:

There have been rare post-marketing reports of anxiety and depression or depressed mood and very rare reports of tics in patients taking ATTENTRA (see **section 4.8**).

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

Serotonin syndrome:

Serotonin syndrome has been reported following concomitant use of atomoxetine, as contained in ATTENTRA, with other serotonergic medicinal products e.g. serotonin-norepinephrine re-uptake inhibitors (SNRIs), selective serotonin re-uptake inhibitors (SSRIs), other SNRIs, triptans, opioids, and tricyclic and tetracyclic antidepressants. If concomitant use of ATTENTRA with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of ATTENTRA therapy should be considered depending on the severity of the symptoms.

Paediatric population under six years of age:

ATTENTRA should not be used in patients less than six years of age as efficacy and safety have not been established in this age group.

The efficacy of ATTENTRA beyond 18 months of treatment and safety of ATTENTRA beyond 2 years of treatment has not been systematically evaluated.

Geriatric use:

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

Other therapeutic use:

ATTENTRA is not indicated for the treatment of major depressive episodes and/or anxiety.

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

Effects on micturition:

The rates of urinary retention and urinary hesitation may be increased.

Urinary retention or urinary hesitancy should be considered potentially related to ATTENTRA.

4.5 Interaction with other medicines and other forms of interaction:

Monoamine oxidase inhibitors (MAOIs):

ATTENTRA should not be used with MAOIs (see **section 4.3**).

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

In patients receiving these medicines, ATTENTRA 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 ATTENTRA 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 ATTENTRA dose has occurred, the clinical response and tolerability should be re-evaluated for that patient to determine if dose adjustment is needed.

Caution is advised when combining ATTENTRA with potent inhibitors of cytochrome P450 enzymes other than CYP2D6 in patients who are poor CYP2D6 metabolisers as the risk of clinically relevant increases in atomoxetine exposure *in vivo* is unknown (see **section 4.8**).

Salbutamol (or other beta-2 agonists):

ATTENTRA should be administered with caution to patients treated with high dose nebulised or

systemically administered salbutamol (or other beta-2 agonists) because cardiovascular effects can be potentiated.

Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either ATTENTRA 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.

Medicines that affect QT prolongation:

There is the potential for an increased risk of QT interval prolongation when atomoxetine 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.

Medicines lowering seizure threshold:

Seizures are a potential risk with ATTENTRA. 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.

Anti-hypertensive medicines:

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

Pressor medicines or medicines that increase blood pressure:

Because of possible increase in effects on blood pressure, ATTENTRA should be used cautiously with

pressor medicines 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 ATTENTRA or pressor agents may be justified in the case of significant change in blood pressure.

Medicines that affect noradrenaline:

Medicines that affect noradrenaline should be used cautiously when co-administered with ATTENTRA 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.

Serotoninergic medicines:

ATTENTRA should be used with caution in combination with serotonergic medicines, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), opioids as tramadol, and tetracyclic or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see **section 4.4**).

Medicines that affect gastric pH:

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

Medicines highly bound to plasma protein:

In vitro medicine-displacement studies were conducted with atomoxetine and other highly-bound medicines at therapeutic concentrations. Warfarin, acetylsalicylic acid, phenytoin or diazepam did not affect the binding of atomoxetine to human albumin. Similarly, atomoxetine did not affect the binding of these compounds to human albumin.

Methylphenidate:

Co‑administration of methylphenidate with ATTENTRA did not increase cardiovascular effects beyond

those seen with methylphenidate administration alone.

Alcohol:

Consumption of ethanol with ATTENTRA did not change the intoxicating effects of ethanol.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety and efficacy have not been demonstrated in pregnancy.

ATTENTRA should not be used during pregnancy.

Lactation:

ATTENTRA and/or its metabolites were excreted in the milk of rats. It is not known if ATTENTRA is excreted in human milk. Women using ATTENTRA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines:

Data on the effects on the ability to drive and use machines are limited. ATTENTRA has a minor influence on the ability to drive and use machines. ATTENTRA has been associated with increased rates of fatigue, somnolence and dizziness relative to placebo in paediatric and adult patients. Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by ATTENTRA (see **section 4.8**).

4.8 Undesirable effects:

Paediatric population:

Summary of the safety profile:

In paediatric trials headache, abdominal pain[1] and decreased appetite are the adverse events most commonly associated with atomoxetine, but seldom lead to medicine discontinuation. 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 atomoxetine recovered to mean weight and height over long-term treatment.

Nausea, vomiting and somnolence[2] can occur in patients, particularly during the first month of therapy. However, these episodes were usually mild to moderate in severity and transient and did not result in a significant number of discontinuations from therapy.

In both paediatric and adult trials, patients taking atomoxetine experienced increases in heart rate, systolic and diastolic blood pressure (see **section 4.4**).

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

TABLE 1: TABULATED SUMMARY OF ADVERSE REACTIONS IN CHILDREN AND ADOLESCENTS

SYSTEM ORGAN CLASS:	FREQUENT:	LESS FREQUENT:	FREQUENCY UNKNOWN:
Metabolism and nutrition disorders:	Decreased appetite, anorexia (loss of appetite)		
Psychiatric disorders:	Irritability, mood swings, insomnia[3], agitation*, anxiety, depression and depressed mood*, tics*	Suicide-related events, aggression, hostility, emotional lability*, psychosis (including hallucinations)*	Bruxism
Nervous system disorders:	Headache, somnolence[2], dizziness	Syncope, tremor, migraine, paraesthesia*, hypoaesthesia*, seizure**	
Eye disorders:	Mydriasis	Vision blurred, conjunctivitis	

Cardiac disorders:		Palpitations, sinus tachycardia, QT interval prolongation**	
Vascular disorders:		Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders:		Dyspnoea*	
Gastrointestinal disorders:	Abdominal pain[1], vomiting, nausea, constipation, dyspepsia		
Hepatobiliary disorders:		Blood bilirubin increased*, abnormal/ increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure*	
Skin and subcutaneous tissue disorders:	Dermatitis, pruritus, rash	Hyperhydrosis, allergic reactions	
Renal and urinary disorders:		Urinary hesitation, urinary retention	
Reproductive system and breast disorders:		Priapism, male genital pain	
General disorders and administration	Fatigue, lethargy, chest pain*	Asthenia	

site conditions:			
Investigations:	Blood pressure increased[4], heart rate increased[4], weight decreased		

[1] Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort

[2] Also includes sedation

[3] Includes initial, middle and terminal (early morning wakening) insomnia

[4] Heart rate and blood pressure findings are based on measured vital signs.

[*] See **section 4.4**

[**] See **section 4.4** and **section 4.5**

CYP2D6 poor metabolisers (PM):

The following adverse events occurred in at least 2 % of CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: appetite decreased; insomnia combined (including insomnia, middle insomnia and initial insomnia); depression combined (including depression, major depression, depressive symptom, depressed mood and dysphoria); weight decreased; constipation; tremor; sedation; excoriation; enuresis; conjunctivitis; syncope; early morning awakening; mydriasis.

The following event did not meet the above criteria but is noteworthy: generalised anxiety disorder. In addition, in trials lasting up to 10 weeks, weight loss was more pronounced in PM patients.

Adults:

Summary of the safety profile:

In adult ADHD clinical trials, the following system organ classes had the highest frequency of adverse

events during treatment with atomoxetine: gastrointestinal, nervous system and psychiatric disorders. The most frequent adverse events reported were appetite decreased, insomnia, headache, dry mouth and nausea. The majority of these events were mild or moderate in severity and the events most frequently reported as severe were nausea, insomnia, fatigue and headache. A complaint of urinary retention or urinary hesitancy in adults should be considered potentially related to atomoxetine.

TABLE 2: TABULATED LIST OF ADVERSE REACTIONS IN ADULTS

SYSTEM ORGAN CLASS:	**FREQUENT:**	**LESS FREQUENT:**
Metabolism and nutrition disorders:	Decreased appetite	
Psychiatric disorders:	Insomnia[2], agitation*, libido decreased, sleep disorder, depression and depressed mood*, anxiety	Suicide-related events*, aggression, hostility and emotional lability*, restlessness, tics *, psychosis (including hallucinations)*
Nervous system disorders:	Headache, dizziness, dysgeusia, paraesthesia, somnolence (including sedation), tremor	Syncope, migraine, hypoaesthesia*, seizure**
Eye disorders:		Blurred vision
Cardiac disorders:	Palpitations, tachycardia	QT interval prolongation**
Vascular disorders:	Flushing, hot flush	Peripheral coldness, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders:		Dyspnoea*

Gastrointestinal disorders:	Dry mouth, nausea, abdominal pain[1], constipation, dyspepsia, flatulence, vomiting	
Hepatobiliary disorders:		Abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure, blood bilirubin increased*
Skin and subcutaneous tissue disorders:	Dermatitis, hyperhydrosis, rash	Allergic reactions[4], pruritus, urticaria
Musculoskeletal and connective tissue disorders:		Muscle spasms
Renal and urinary disorders:	Dysuria, pollakiuria, urinary hesitation, urinary retention	Micturition urgency
Reproductive system and breast disorders:	Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, male genital pain	Ejaculation failure, menstruation irregular, orgasm abnormal, priapism
General disorders and administration site conditions:	Asthenia, fatigue, lethargy, chills, feeling jittery, irritability, thirst	Feeling cold, chest pain*

Investigations:	Blood pressure increased[3], heart rate increased[3], weight decreased	

[1] Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort

[2] Also includes initial insomnia, middle insomnia and terminal (early morning wakening) insomnia

[3] Heart rate and blood pressure findings are based on measured vital signs

[4] Includes anaphylactic reactions and angioneurotic oedema

[*] See **section 4.4**

[**] See **section 4.4** and **section 4.5**

CYP2D6 poor metabolisers (PM):

The following adverse events occurred in at least 2 % of CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: vision blurred, dry mouth, constipation, feeling jittery, decreased appetite, tremor, insomnia, sleep disorder, middle insomnia, terminal insomnia, urinary retention, erectile dysfunction, ejaculation disorder, hyperhidrosis, peripheral coldness.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose:

Signs and symptoms:

There have been reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most commonly reported symptoms accompanying acute and chronic overdoses were gastrointestinal symptoms, somnolence, dizziness, tremor and abnormal behaviour. Hyperactivity and agitation have also been reported. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g. tachycardia, blood pressure increased, mydriasis, dry mouth) were also observed and reports of pruritus and rash have been received. Most events were mild to moderate.

In some cases of overdose involving atomoxetine, seizures have been reported and very rarely QT prolongation and serotonin syndrome have been reported.

There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other medicine.

There is limited clinical trial experience with atomoxetine overdose.

Management:

An airway should be established. Activated charcoal may be useful in limiting absorption if the patient presents within 1 hour of ingestion. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. The patient should be observed for a minimum of 6 hours. Because atomoxetine 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 highly selective and potent inhibitor of the pre-synaptic noradrenaline 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 compound 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 six years of age.

Pharmacokinetic studies have shown that atomoxetine capsules and oral solution are bioequivalent.

Absorption:

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

Distribution:

Atomoxetine is widely distributed and is extensively (98 %) bound to plasma proteins, primarily albumin.

Biotransformation:

Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. Individuals with reduced activity of this pathway (poor metabolisers) represent about 7 % of the Caucasian population and have higher plasma concentrations of atomoxetine compared to people with normal activity (extensive metabolisers). For poor metabolisers, AUC of atomoxetine is approximately 10-fold greater and $C_{ss,\ max}$ is about 5-fold greater than extensive metabolisers. Atomoxetine does not inhibit or induce CYP2D6 at therapeutic doses.

Cytochrome P450 Enzymes: Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6 and CYP2C9.

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.

Special patient populations:

Hepatic impairment results in a reduced atomoxetine clearance, increased atomoxetine exposure and a prolonged half-life of parent compound compared to healthy controls with the same CYP2D6 extensive metaboliser genotype. In patients with moderate to severe hepatic impairment (Child-Pugh class B and C) initial and target doses should be adjusted (see **section 4.2**).

Pharmacokinetics of atomoxetine and its metabolites in individuals with end-stage renal disease (ESRD) suggests that no dose adjustment would be necessary (see **section 4.2**).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule content:

Co-processed maize starch consisting of maize starch and pregelatinised starch

Dimethicone 350 cs

Sodium starch glycolate (type A)

Capsule shell:

Gelatin

Titanium dioxide

For 18 mg: yellow iron oxide (E172)

For 25 mg and 40 mg: indigotine (E132) and black iron oxide (E172)

For 60 mg: indigotine (E132), black iron oxide (E172) and yellow iron oxide (E172)

For 80 mg: yellow iron oxide (E172) and red iron oxide (E172)

Printing ink:

Shellac

Propylene glycol

Ammonia solution

Black iron oxide (E172)

Potassium hydroxide

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

PVC/PVdC/PVC/Alu blisters: 3 years.

HDPE bottles: 3 years.

Proposed in-use shelf life: 6 months after first opening is proposed.

6.4 Special precautions for storage:

Store at or below 25 °C.

6.5 Nature and contents of container:

Opaque PVC/PVdC/PVC & aluminium blister strips in an outer cardboard carton.

White HDPE container with white polypropylene closure.

Pack sizes: 7, 14, 28, 30, 56, 60, 100, 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

The capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of the capsules 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

South Africa,

2090

8. REGISTRATION NUMBERS:

ATTENTRA 10: 50/1.2/0591

ATTENTRA 18: 50/1.2/0592

ATTENTRA 25: 50/1.2/0593

ATTENTRA 40: 50/1.2/0594

ATTENTRA 60: 50/1.2/0595

ATTENTRA 80: 50/1.2/0596

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

11 August 2020

10. DATE OF REVISION OF THE TEXT:

9 July 2025