Approved Professional Information for Medicines for Human Use:

CONCITRON 10 /18 /25 /40 /60 /80 mg

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

CONCITRON 10 MG Capsules

CONCITRON 18 MG Capsules

CONCITRON 25 MG Capsules

CONCITRON 40 MG Capsules

CONCITRON 60 MG Capsules

CONCITRON 80 MG Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CONCITRON 10 MG

Each hard gelatine capsule contains 10 mg atomoxetine.

CONCITRON 18 MG

Each hard gelatine capsule contains 18 mg atomoxetine.

CONCITRON 25 MG

Each hard gelatine capsule contains 25 mg atomoxetine.

CONCITRON 40 MG

Each hard gelatine capsule contains 40 mg atomoxetine.

CONCITRON 60 MG

Each hard gelatine capsule contains 60 mg atomoxetine.

CONCITRON 80 MG

Each hard gelatine capsule contains 80 mg atomoxetine.

Sugar free.

For the full list of excipients, see section 6.1.

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

CONCITRON (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (AHDH). Anyone considering the use of CONCITRON 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. CONCITRON is approved for ADHD in paediatric and adult patients. CONCITRON is not approved for major depressive disorder.

3. PHARMACEUTICAL FORM

Hard gelatine capsules.

CONCITRON 10 MG

Hard gelatine, white capsules with overprint on the body: 10 mg

CONCITRON 18 MG

Hard gelatine capsules with white body and yellow cap, with overprint

on the body: 18 mg

CONCITRON 25 MG

Hard gelatine capsules with white body and blue cap, with overprint

on the body: 25 mg

CONCITRON 40 MG

Hard gelatine, blue capsules with overprint of the body: 40 mg

CONCITRON 60 MG

Hard gelatine capsules with yellow body and blue cap, with overprint

on the body: 60 mg

CONCITRON 80 MG

Hard gelatine capsules with white body and brown cap, with overprint

on the body: 80 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CONCITRON 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

Posology

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

CONCITRON should not be exceeded because of potential side effects (See section 4.8).

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

CONCITRON 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.

CONCITRON may be discontinued without tapering the dose.

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 from 384 patients with up to 97 weeks of treatment with CONCITRON 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 CONCITRON in any 24 - hour period.

Special Populations

Renal / Hepatic Impairment

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

Elderly population

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

Paediatric population ≤ six years

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

Method of administration

CONCITRON may be taken with or without food.

CONCITRON may be discontinued without tapering the dose.

CONCITRON capsules are not intended to be opened. CONCITRON 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.

4.3 Contraindications

- Hypersensitivity to atomoxetine hydrochloride or to any of the excipients listed in section 6.1.
- CONCITRON should not be used in patients with uncontrolled hypertension or impairment of liver function.
- Monoamine oxidase inhibitors: CONCITRON should not be used in combination with monoamine oxidase inhibitors (MAOIs), including linezolid. (See section 4.5).

  CONCITRON 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 CONCITRON.
- Severe Cardiovascular Disorders: CONCITRON 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 in 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).

- Phaeochromocytoma: CONCITRON should not be used in patients with phaeochromocytoma or a history of phaeochromocytoma (see section 4.4).
- Narrow angle glaucoma: In clinical studies, the use of CONCITRON was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

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. a paediatrician or child/adolescent psychiatrist).

Suicide-related behaviour

Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double-blind clinical trials, suicide-related behaviours were less frequent, but more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo, where there were no events. In adult double-blind clinical trials, there was no difference in the frequency of suicide-related behaviour between atomoxetine and placebo. Patients who are being treated with CONCITRON 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 atomoxetine at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, CONCITRON should only be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

Cardiovascular effects

Atomoxetine can affect heart rate and blood pressure. Most patients taking atomoxetine experience a modest increase in heart rate (mean < 10 bpm) and/or increase in blood pressure (mean < 5 mm Hg) (see section 4.8). However, combined data from controlled and uncontrolled ADHD clinical trials show that approximately 8 – 12 % of children and adolescents, and 6 – 10 % of adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15 - 20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15 – 26 % of children and adolescents, and 27 – 32 % of adults experiencing such changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases. 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 atomoxetine 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 with CONCITRON 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.

CONCITRON should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.3).
Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the

dysfunction of ion channels). Severe cerebrovascular disorders may include cerebral aneurysm or stroke.

CONCITRON should be used with caution in patients with:

- 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.
- develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.
- congenital or acquired long QT or a family history of QT prolongation (see sections 4.5).
- any condition that may predispose patients to hypotension or conditions associated with abrupt heart rate or blood pressure changes (as orthostatic hypotension has also been reported)

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 CONCITRON.

Hepatic effects

CONCITRON should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.

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.

Psychotic or manic symptoms

The possibility that CONCITRON will cause the exacerbation of pre-existing psychotic or manic symptoms cannot be excluded.

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 atomoxetine, and discontinuation of CONCITRON should be considered.

Aggressive behaviour, hostility or emotional lability

Patients taking CONCITRON should be closely monitored for the appearance or worsening of 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 atomoxetine compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with atomoxetine compared to those treated with placebo.

Possible allergic events

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

Seizures

CONCITRON should be used with caution in patients with a history of seizures as seizures are a potential risk with atomoxetine. Discontinuation of CONCITRON should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.

Growth and development

Growth and development should be monitored in children and adolescents during treatment with CONCITRON. 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. Therefore, patients requiring long-term therapy should be carefully monitored.

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

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

In a controlled study of paediatric patients with ADHD and comorbid chronic motor tics or Tourette's Disorder, atomoxetine-treated patients did not experience worsening of tics compared to placebo-treated patients. In a controlled study of adolescent patients with ADHD and comorbid Major Depressive Disorder, atomoxetine-treated patients did not experience worsening of depression compared to placebo-treated patients. In two controlled studies (one in paediatric patients and one in adult patients) of patients with ADHD and comorbid anxiety disorders,
atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

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

Raynaud’s phenomenon

CONCITRON should not be used in patients with Raynaud’s phenomenon.

Effects on micturition

As per reported adult ADHD controlled trials, the rates of urinary retention and urinary hesitation were increased among the atomoxetine subjects compared with placebo subjects. A complaint of urinary retention or urinary hesitancy should be considered potentially related to CONCITRON.

Other therapeutic use

CONCITRON is not indicated for the treatment of major depressive episodes and/or anxiety as the results of clinical trials in adults in these conditions, where ADHD is not present, did not show an effect compared to placebo (see section 5.1).

Special populations

Paediatric use

The safety and efficacy of CONCITRON in paediatric patients less than 6 years of age have not been established. The efficacy of CONCITRON beyond 18 months of treatment and safety of CONCITRON beyond 2 years of treatment has not been systematically evaluated.

Elderly use

The safety and efficacy of CONCITRON in elderly patients have not been established.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on atomoxetine

MAOI's

CONCITRON should not be used with MAOI's (see section 4.3).

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

Caution is advised when combining CONCITRON 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).

In patients receiving treatment with atomoxetine, exposure may be 6- to 8- fold increased and Css max 3 to 4 times higher, because it is metabolised by the CYP2D6 pathway. Slower titration and final lower dosage of atomoxetine 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 CONCITRON 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 beta2 agonists)

CONCITRON should be administered with caution to patients treated with high dose nebulised or systemically administered salbutamol (or other beta2 agonists) because cardiovascular effects can be potentiated.

Contradictory findings regarding this interaction were found. Systemically administered salbutamol (600 µg i.v. over 2 hrs) in combination with atomoxetine (60 mg twice daily for 5 days) induced increases in heart rate and blood pressure. This effect was most marked after the initial coadministration of salbutamol and atomoxetine but returned towards baseline at the end of 8 hours. However, in a separate study the effects on blood pressure and heart rate of a standard inhaled dose of salbutamol (200 µg) were not increased by the short-term coadministration of atomoxetine (80 mg once daily for 5 days) in a study of healthy Asian adults who were extensive atomoxetine metabolisers.

Similarly, heart rate after multiple inhalations of salbutamol (800 µg) did not differ in the presence or absence of atomoxetine.

Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either atomoxetine or salbutamol (or other beta2 agonists) in the event of significant increases in heart rate and blood pressure during coadministration of CONCITRON and salbutamol.

Medicine 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.

Medicine lowering seizure threshold

Seizures are a potential risk with atomoxetine. Caution is advised with concomitant use of medicinal agents 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

CONCITRON 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 used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of CONCITRON or anti-hypertensive medicines may be justified in the case of significant changes of blood pressure.

Pressor agents or medicines that increase blood pressure

Because of possible increase in effects on blood pressure, CONCITRON should be used cautiously with pressor agents or medications that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either CONCITRON 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 CONCITRON 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 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 drug-displacement studies were conducted with atomoxetine and other highly bound substances 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

Reported co-administration of methylphenidate with atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Alcohol

Reported consumption of ethanol with atomoxetine did not change the intoxicating effects of ethanol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in treatment with CONCITRON haves not been demonstrated in pregnancy. Atomoxetine should not be used during pregnancy.

Breastfeeding

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Because of the lack of data, CONCITRON should be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

CONCITRON has a minor influence on the ability to drive and use machines. Atomoxetine 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 atomoxetine.

4.8 Undesirable effects

Paediatric population

a) Summary of the safety profile

In reported paediatric trials, headache, abdominal pain and decreased appetite are the adverse events most commonly associated with atomoxetine, but seldom lead to drug 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 as predicted by group baseline data over the 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.

b) Tabulated summary of adverse reactions in children and adolescents

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Metabolism and nutrition disorders	Appetite decreased 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) *	
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 (see section 4.4)	
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, pruritis, rash	Hyperhydrosis, allergic reactions	
Renal and urinary disorders		Urinary hesitation, urinary retention	
Reproductive system and breast disorders		Priapism, male genital pain	
General disorders and	Fatigue, lethargy, chest pain (see section 4.4)	Asthenia	

administration 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

c. Description of selected adverse reactions

CYP2D6 poor metabolisers (PM):

The following reported adverse occurred 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 reported trials lasting up to 10 weeks, weight loss was more pronounced in PM patients.

Adults

a) Summary of the safety profile

In reported 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.

b) Tabulated summary ~~list~~ of adverse reactions in adults

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Metabolism and nutrition disorders	Appetite decreased		
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 (see section 4.4)	
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], pruritis, urticaria	
Musculoskeletal and connective tissue disorders		Muscle spasms	
Renal and urinary disorders	Dysuria, pollakuria, urinary hesitation, urinary retention	Micturation urgency	

Reproductive system and breast disorders	Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, male genital pain	Ejaculation failure, menstruation irregular, orgasm abnormal Priaprism	
General disorders and administration site conditions	Asthenia, fatigue, lethargy, chills, feeling jittery, irritability, thirst	Feeling cold, chest pain (see section 4.4)	
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

c. Description of selected adverse reactions

CYP2D6 poor metabolisers (PM)

The following adverse events were reported 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 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

4.9 Overdose

Signs and symptoms

During post-marketing, there have been reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most frequently 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 less frequently QT prolongation. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other medicinal agent.

There is limited clinical trial experience with atomoxetine overdose.

Management

An open 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

Pharmacological Classification/Category and Class: A1.2 Psychoanaleptics

Pharmacotherapeutic group: Psychoanaleptics, centrally acting sympathomimetics.

ATC code: N06BA09.

Mechanism of action

Atomoxetine is a selective inhibitor of the pre-synaptic noradrenaline transporter, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

5.2 Pharmacokinetic properties

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

Absorption

Atomoxetine is well absorbed after oral administration, reaching mean maximal observed plasma concentration (Cmax) approximately 1 to 2 hours after dosing. The absolute bioavailability of atomoxetine following oral administration ranged from 63 % to 94 %, depending upon inter-individual differences in the modest first-pass metabolism. 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 with people with normal activity (extensive metabolisers). For poor metabolisers, AUC of atomoxetine is approximately 10-fold greater and Cmax is about 5-fold greater than extensive metabolisers. 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 CYP2D6 at therapeutic doses.
Other Cytochrome P450 Enzymes: Atomoxetine did not cause clinically significant inhibition or induction of other cytochrome P450 enzymes, including CYP1A2, CYP3A, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Starch, pregelatinized; croscarmellose sodium; silica, colloidal anhydrous; magnesium stearate.

Capsule shell

Gelatine; titanium dioxide (E171); yellow iron oxide (E172); indigotine (E132); black iron oxide (E172); red iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Capsules: 36 months.

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

Capsules: Al /PVC /PCTFE blisters sealed with aluminium foil and are packed into cartons of 28's or 30's.

Not all pack sizes may be marketed.

6.6 Special precautions for other handling

The capsules are not intended to be opened.

Atomoxetine is an ocular irritant. In the event of the capsules content coming in 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

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

CONCITRON 10 /18 /25 /40 /60 /80 mg Capsules: 50/1.2/9002, 50/1.2/9003, 50/1.2/9004, 50/1.2/9005, 50/1.2/9006, 50/1.2/9007.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 December 2020

10. DATE OF REVISION OF THE TEXT

28 October 2021