CLEAN PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ESCITALOPRAM UNICORN 5 mg film coated tablets

ESCITALOPRAM UNICORN 10 mg film coated tablets

ESCITALOPRAM UNICORN 15 mg film coated tablets

ESCITALOPRAM UNICORN 20 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ESCITALOPRAM UNICORN 5:

Each film coated tablet contains escitalopram oxalate equivalent to 5 mg escitalopram.

ESCITALOPRAM UNICORN 10:

Each film coated tablet contains escitalopram oxalate equivalent to 10 mg escitalopram.

ESCITALOPRAM UNICORN 15:

Each film coated tablet contains escitalopram oxalate equivalent to 15 mg escitalopram.

ESCITALOPRAM UNICORN 20:

Each film coated tablet contains escitalopram oxalate equivalent to 20 mg escitalopram.

ESCITALOPRAM UNICORN is sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

ESCITALOPRAM UNICORN 5:

White, round, biconvex, film coated tablet, debossed with ‘B2’ on one side and plain on the other side.

ESCITALOPRAM UNICORN 10:

White, oval shaped, biconvex, film coated tablet, with score-line on one side, debossed with ‘B’ on left side of score-line and ‘3’ on right side of score-line and plain on the other side.

ESCITALOPRAM UNICORN 15:

White, modified capsule shaped, biconvex, film coated tablet with score-line on both sides, debossed with ‘15’ on one side of the score-line, on one side of the tablet.

ESCITALOPRAM UNICORN 20:

White, oval shaped, biconvex, film coated tablet with score-line on one side, debossed with ‘B4’ on side of score-line and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ESCITALOPRAM UNICORN is indicated for the treatment of

- Major depressive episodes.
- Panic disorder with or without agoraphobia.

4.2 Posology and method of administration

Posology

Major depressive episodes

A single oral dose of 10 mg per day in otherwise healthy adults. Dosage may be increased to a maximum of 20 mg per day, depending on the patient’s response. A treatment period of 2 to 4 weeks is usually required for an antidepressant effect.

Panic disorder with or without agoraphobia

A single oral dose of 5 mg per day for the first week, before increasing it to a 10 mg daily dose. The dose may be further increased thereafter as required to a maximum of 20 mg per day depending on the patient's response.

The onset of action is seen within 2 to 4 weeks. Treatment should be continued for an appropriate length of time (up to six months) after recovery in order to prevent relapse. **ESCITALOPRAM UNICORN** should be gradually withdrawn during a couple of weeks when stopping therapy (see sections 4.4, 4.8).

Special populations

Elderly: In view of a decreased metabolism, clearance and longer half-life, the initial and maximum dose should be lower than the adult recommended dose.

Reduced hepatic function: Dose should be halved to the lower end of the dosage range.

Reduced renal function: Dose adjustment is not necessary in cases of mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Paediatric population

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events, such as suicidal ideation and self-harm (see sections 4.4, 4.8).

Method of administration

ESCITALOPRAM UNICORN may be taken with or without food in the morning or evening.

4.3 Contraindications

- Hypersensitivity to escitalopram or any of the ingredients in the formulation (see sections 2, 6.1).
- Patients with known QT interval prolongation or congenital long QT syndrome.

- Concurrent use with medicines such as pimozide that are known to prolong the QT interval (see section 4.5).
- Concurrent use with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between discontinuing the MAOI and initiating therapy with **ESCITALOPRAM UNICORN**. MAOIs should not be introduced for 7 days after discontinuation of **ESCITALOPRAM UNICORN** (see section 4.5).
- Safety and efficacy in pregnancy and lactation have not been established.
- Children under the age of 18 years (see sections 4.4, 4.8).

4.4 Special warnings and precautions for use

ESCITALOPRAM UNICORN should be used with caution in:

- *Elderly patients* – Longer half-life and decreased clearance due to a reduced rate of metabolism. A lower dose is recommended in the elderly.
- *Hepatic impairment* – Clearance of **ESCITALOPRAM UNICORN** is reduced. Cautious dosage titration and a lower maximum dose are recommended.
- *Seizures or history thereof* – There is an increased risk of seizures. **ESCITALOPRAM UNICORN** should be used with caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. **ESCITALOPRAM UNICORN** should be discontinued in any patient who develops seizures.
- *Electroconvulsive therapy* – Caution is advised in patients receiving electroconvulsive therapy as there is limited clinical experience of concurrent administration of **ESCITALOPRAM UNICORN** and electroconvulsive therapy.
- *Mania or history of mania* – Condition may be re-activated. **ESCITALOPRAM UNICORN** should be used with caution in patients with a history of mania/hypomania. **ESCITALOPRAM UNICORN** should be discontinued if the patient enters the manic phase.

- *Coronary heart disease* – **ESCITALOPRAM UNICORN** may cause a reduction in heart rate. Caution is advised in patients with pre-existing slow heart rates or in patients with acute myocardial infarction or uncompensated heart failure.
- *Diabetes mellitus* – Hypoglycaemia has been reported. Insulin and/or hypoglycaemic dosage may need to be adjusted.
- *Suicide/suicidal thoughts or clinical worsening* – Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **ESCITALOPRAM UNICORN** should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy, or at any time of dose changes, either increases or decreases.

  Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

  The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **ESCITALOPRAM UNICORN**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
- *Haemorrhage* – There have been reports of cutaneous bleeding time increases and/or bleeding abnormalities, such as ecchymoses, gynaecological haemorrhages, gastrointestinal

bleeding and other cutaneous or mucous bleeding with **ESCITALOPRAM UNICORN**. SSRIs/SNRI's may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to **ESCITALOPRAM UNICORN** (see sections 4.6, 4.8).

- *Discontinuation symptoms seen when stopping **ESCITALOPRAM UNICORN** treatment* – If the decision is made to discontinue treatment, **ESCITALOPRAM UNICORN** should be tapered (see section 4.2) in order to prevent the possibility of a withdrawal syndrome.
- *Paediatric population* – Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events, such as suicidal ideation and self-harm (see sections 4.3, 4.8).
- *Paradoxical anxiety* – Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with **ESCITALOPRAM UNICORN**. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect (see section 4.2).
- *Akathisia/psychomotor restlessness* – The use of **ESCITALOPRAM UNICORN** has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose can be detrimental.
- *Hyponatraemia* – Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion, has been reported with the use of selective serotonin re-uptake inhibitors (SSRIs) and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as the elderly, or patients with cirrhosis, or if used in combination with other medications which may cause hyponatraemia.
- *Serotonin syndrome* – Caution is advisable if **ESCITALOPRAM UNICORN** is used concomitantly with medicines with serotonergic effects, such as sumatriptan or other triptans, tramadol or tryptophan. Serotonin syndrome has been reported in patients using SSRIs

concomitantly with serotonergic medicines and is more likely to occur after an increase in dose. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs, treatment with the SSRI and the serotonergic medicine should be discontinued immediately and symptomatic treatment initiated.

- *QT interval prolongation* – **ESCITALOPRAM UNICORN** may cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia, including torsades de pointes have been reported during the post-marketing period, predominantly in female patients with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8).

  Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

  Electrolyte disturbances, such as hypokalaemia and hypomagnesaemia, increase the risk for malignant dysrhythmias and should be corrected before treatment with **ESCITALOPRAM UNICORN** is started.

  If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

  If signs of cardiac dysrhythmia occur during treatment with **ESCITALOPRAM UNICORN**, the treatment should be withdrawn and an ECG should be performed.
- *St John's wort* – Concomitant use of SSRIs and herbal remedies containing St John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.8).
- *Angle-closure glaucoma* – **ESCITALOPRAM UNICORN** may have an effect on pupil size, resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle, resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. **ESCITALOPRAM UNICORN** should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

4.5 Interaction with other medicines and other forms of Interaction

- **Monoamine oxidase inhibitors (MAOI) e.g., linezolid, selegiline, moclobemide** – Concurrent use is contra-indicated. Serious and potentially fatal reactions resembling serotonin syndrome have occurred, such as hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuation of vital signs and mental status changes, including extreme agitation progressing to delirium and coma (see section 4.3).
- **Imipramine** – An increase in the concentration of desimipramine (the active metabolite of imipramine) may occur.
- **Other serotonergic medicines or medicines with serotonergic activity e.g., tramadol, sumatriptan and other triptans** – Increased risk of developing serotonin syndrome, a rare but potentially fatal hyper serotonergic state.
- **Alcohol** – The effects of alcohol may be increased and should be avoided.
- **Anticoagulants, e.g., warfarin** – The anticoagulant activity of warfarin may be increased.
- **Cimetidine** – The AUC and the maximum plasma concentration of **ESCITALOPRAM UNICORN** are increased when **ESCITALOPRAM UNICORN** is administered concurrently with cimetidine.
- **QT interval prolongation** – Co-administration of **ESCITALOPRAM UNICORN** with medicines that prolong the QT interval, such as class IA and III antidysrhythmics, antipsychotics (e.g., phenotiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g., sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), is contraindicated.
- **Medicines lowering the seizure threshold** – SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold (e.g., antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol).

- **Lithium, tryptophan** – There have been reports of enhanced effects when SSRIs have been given together with lithium or tryptophan. Concomitant use of SSRIs with these medicines should therefore be undertaken with caution.
- **St John's wort** – Concomitant use of SSRIs and herbal remedies containing St John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.4).
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** – Concomitant use of NSAIDs may increase bleeding-tendency (see section 4.4).
- **Medicines inducing hypokalaemia/hypomagnesaemia** – Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicines, as these conditions increase the risk of malignant dysrhythmias (see section 4.4).
- **Influence of other medicines on the pharmacokinetics of escitalopram** – The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism, although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.
  Co-administration of **ESCITALOPRAM UNICORN** with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in a moderate increase in the plasma concentration of escitalopram.
- **Effect of ESCITALOPRAM UNICORN on the pharmacokinetics of other medicines** – Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when **ESCITALOPRAM UNICORN** is co-administered with medicines that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g., flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicines that are mainly metabolised by CYP2D6, e.g., antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine or metoprolol resulted in both cases in a twofold increase in the plasma levels of these two CYP2D6 substrates.

In vitro studies have demonstrated that escitalopram may also cause weak inhibition of CYP2C19. Caution is recommended with concomitant use of medicines that are metabolised by CYP2C19.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established (see section 4.3).

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

ESCITALOPRAM UNICORN is excreted into the breast milk.

4.7 Effects on ability to drive and use machines

ESCITALOPRAM UNICORN may impair performance of skilled tasks. If affected these patients should not operate machinery or drive.

4.8 Undesirable effects

Blood and the lymphatic system disorders:

Frequency unknown: Thrombocytopenia

Immune system disorders:

Less frequent: Anaphylactic reaction

Frequency unknown: Angioedema

Metabolism and nutrition disorders:

Frequent: Decreased appetite, increased

appetite, increased mass

Less frequent: Decreased mass

Frequency unknown: Hyponatraemia, anorexia, hypoglycaemia, inappropriate ADH secretion

Psychiatric disorders:

Frequent: Anxiety, restlessness, abnormal dreams, decreased libido, anorgasmia (in females)

Less frequent: Bruxism, nervousness, panic attack, aggression, depersonalisation, hallucinations, agitation, confusion, mania

Frequency unknown: Suicidal ideation, suicidal behaviour, hostility, self-harm

Nervous system disorders:

Frequent: Sleep disturbances, insomnia, somnolence, dizziness, fatigue, headache, paraesthesia, tremor

Less frequent: Taste disturbance, sleep disorder, syncope, serotonin syndrome, restlessness, impaired concentration, malaise, convulsions, neuroleptic malignant syndrome, dyskinesia movement disorder, psychomotor restlessness/akathisia

Eye disorders:

Less frequent: Accommodation (visual) disturbances, mydriasis

Ear and labyrinth disorders:

Less frequent: Tinnitus

Cardiac disorders:

Less frequent: Tachycardia, palpitations, bradycardia, prolonged electrocardiogram QT interval, ventricular dysrhythmia (including torsades de pointes)

Vascular disorders:

Frequency unknown: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Frequent: Sinusitis, yawning

Less frequent: Nasal congestion, epistaxis

Gastrointestinal disorders:

Frequent: Nausea, constipation, diarrhoea, dry mouth, dyspepsia, vomiting

Less frequent: Gastrointestinal haemorrhage (including rectal haemorrhage)

Frequency unknown: Salivation

Hepato-biliary disorders:

Frequency unknown: Hepatitis, abnormal liver function tests

Skin and subcutaneous tissue disorders:

Frequent: Increased sweating

Less frequent: Urticaria, alopecia, pruritus, rash

Frequency unknown: Ecchymosis

Musculoskeletal, connective tissue and bone disorders:

Frequent: Asthenia, arthralgia, myalgia

Frequency unknown: Increased risk of bone fractures (class effect of SSRIs, like **ESCITALOPRAM UNICORN**)

Renal and urinary disorders:

Frequency unknown: Micturition disorders, urinary Retention

Reproductive system and breast disorders:

Frequent: Sexual dysfunction (including ejaculation disorder), decreased libido, impotence

Less frequent: Metrorrhagia, menorrhagia, galactorrhoea, priapism

Frequency unknown: Postpartum haemorrhage*

*This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

General disorders:

Frequent: Pyrexia, oedema

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to

enquiries@unicornpharma.co.za.

4.9 Overdose

Symptoms of overdose:

Tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence and sinus tachycardia (see also sections 4.4, 4.8).

Treatment of overdose:

Treatment is symptomatic and supportive.

There is no specific antidote to **ESCITALOPRAM UNICORN**.

The stomach should be emptied as soon as possible by emesis or gastric lavage. Monitoring of cardiac and vital signs is necessary, and medical surveillance is advisable for about 24 hours, along with general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

Escitalopram is the (*S*)-enantiomer of citalopram, a bicyclic phthalane derivative with antidepressant effect. Its effect is linked to the selective inhibition of specific serotonin (5-HT) re-uptake. Escitalopram blocks 5-HT re-uptake, leading to potentiation of serotonergic activity in the central nervous system (CNS). Escitalopram does not have an effect on noradrenaline, dopamine and gamma aminobutyric acid (GABA) re-uptake. Escitalopram also has little or no antidopaminergic, antiadrenergic, antiserotonergic, antihistaminergic or anticholinergic properties

5.2 Pharmacokinetic properties

After oral administration of single or multiple doses, the absorption of escitalopram was relatively fast, with maximum plasma levels reached in 2 to 4 hours. Elimination half-life of escitalopram is between 27 and 33 hours while its steady state was attained within 7 to 10 days. The absorption of escitalopram is not influenced by food intake. The area under the plasma or serum

concentration time curve from time zero to 24 hours and $C_{(max)}$ was both linear and proportional to the dose of escitalopram. The volume of distribution of escitalopram is about 20 l/kg and binds approximately 55 % to plasma proteins. Demethylated and did methylated metabolites of escitalopram are produced in the liver as well as an *N*-oxide metabolite. Cytochrome P450 CYP3A4, CYP2C19 and CYP2D6 enzymes are involved in the metabolism of escitalopram. The primary route of elimination of escitalopram is as metabolites via the urine. Longer half-lives and decreased clearance of escitalopram due to reduced rate of metabolism have been demonstrated in the elderly and in patients with reduced liver function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry White (containing macrogol, hypromellose and titanium dioxide) and talcum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

ESCITALOPRAM UNICORN is packed into transparent PVC/PE/PVDC film / silver aluminum foil blister strips or OPA-Alu-PVC/Alu / silver aluminum foil blister strips.

10 or 14 film coated tablets are packed per blister strip.

2 x 14 tablet blister strips (28 film coated tablets) or 3 x 10 tablet blister strips (30 film coated tablets) are packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd.

Cnr. Searle & Pontac Streets,

Cape Town, 8001

South Africa

8 REGISTRATION NUMBERS

ESCITALOPRAM UNICORN 5: 46/1.2/0340

ESCITALOPRAM UNICORN 10: 46/1.2/0341

ESCITALOPRAM UNICORN 15: 46/1.2/0342

ESCITALOPRAM UNICORN 20: 46/1.2/0343

9 DATE OF FIRST AUTHORISATION

26 November 2015

10 DATE OF REVISION OF TEXT

01 August 2021