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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Accord Escitalopram 10 (film-coated tablets)

Accord Escitalopram 20 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Accord Escitalopram 10: Each film-coated tablet contains: Escitalopram oxalate equivalent to 10 mg escitalopram.

Accord Escitalopram 20: Each film-coated tablet contains: Escitalopram oxalate equivalent to 20 mg escitalopram.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Accord Escitalopram 10: White to off-white, oval, biconvex, film-coated tablets with an inscription of '1' and '0' on either side of the break-line and plain on the other side.

Accord Escitalopram 20: White to off-white, oval, biconvex, film-coated tablets with a break-line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accord Escitalopram is indicated for:

Treatment of major depressive episodes.

Treatment of panic disorder with or without agoraphobia.

Treatment of social anxiety disorder (social phobia).

Treatment of generalised anxiety disorder.

Treatment of obsessive-compulsive disorder.

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4.2 Posology and method of administration

Posology

Adults:

Major depressive episodes:

Accord Escitalopram should be administered as a single oral dose of 10 mg daily in otherwise healthy adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Usually two to four weeks are necessary for an anti-depressant response.

Panic disorder with or without agoraphobia:

A single oral dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response. Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder:

Usual dosage is 10 mg once daily. The dose may be increased to a maximum of 20 mg daily depending on individual patient response.

Usually 2-4 weeks are necessary to obtain symptom relief. Treatment for 3 months is recommended to consolidate response. Long-term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis. Treatment benefits should be re-evaluated at regular intervals.

Generalised anxiety disorder:

Recommended dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Long term treatment of responders has been studied for at least 6 months and can be considered on an individual basis to prevent relapse.

Obsessive-compulsive disorder:

Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to 20 mg daily.

Long-term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 or 20 mg/day.

As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Withdrawal reactions:

When stopping Accord Escitalopram therapy, gradual dose reduction should be considered.

Special populations

Elderly patients (> 65 years of age):

A longer half-life and a decreased clearance have been demonstrated in the elderly, therefore a lower initial and maximum dose should be considered.

Reduced renal function:

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

Reduced hepatic function:

Dosages should be halved to the lower end of the dose range in patients with hepatic insufficiency. (see section 4.4)

Children and adolescents (< 18 years)

Children under the age of 18 years, as safety and efficacy have not been established in this population. (see section 4.3)

Method of administration

Accord Escitalopram is administered as a single daily dose. Accord Escitalopram may be taken with or without food.

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4.3 Contraindications

Accord Escitalopram is contra-indicated in:

- Patients with hypersensitivity to escitalopram or to any of the excipients listed in section 6.1.
- Children under the age of 18 years, as safety and efficacy have not been established in this population.
- Monoamine Oxidase Inhibitors (MAOI): Cases of serious reactions have been reported in patients receiving an SSRI (selective serotonin re-uptake inhibitor) such as Accord Escitalopram in combination with a MAOI, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see section 4.5). Some cases presented with features resembling serotonin syndrome (see section 4.6). Accord Escitalopram should not be used in combination with a MAOI. Accord Escitalopram may be started 14 days after discontinuing treatment with a MAOI. At least 7 days should elapse after discontinuing Accord Escitalopram treatment before starting a MAOI.
- Concomitant treatment with linezolid.
- Concomitant treatment with pimozide as the combination may lead to clinically significant QTRC prolongation.
- Accord Escitalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.

4.4 Special warnings and precautions for use

Mania:

Accord Escitalopram should be discontinued in any patient entering a manic phase. Accord Escitalopram should be used with caution in patients with a history of mania/hypomania.

Paradoxical anxiety:

Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with Accord Escitalopram. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures:

Accord Escitalopram should be discontinued in any patient who develops seizures. Accord Escitalopram should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be closely monitored. Accord Escitalopram should be discontinued if there is an increase in seizure frequency.

Diabetes mellitus:

In patients with diabetes mellitus, treatment with Accord Escitalopram may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Haemorrhage:

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with escitalopram. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking Accord Escitalopram, particularly in concomitant use with medicines known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicines (NSAIDs), as well as in patients with a history of bleeding disorders.

ECT (electroconvulsive therapy):

There is limited published clinical experience of concurrent administration of Accord Escitalopram and ECT, therefore caution is advisable.

Suicide:

As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicidal attempt is inherent in depression and may persist until significant therapeutic effect is achieved.

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 medicine in inducing such behaviour has not been established. Patients being treated

with Accord Escitalopram 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 disorders 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 such as Accord Escitalopram 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 suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing Accord Escitalopram, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, Accord Escitalopram should be tapered (See section 4.2 and section 4.4).

Serotonin syndrome:

Caution is advisable if Accord Escitalopram is used concomitantly with medicines with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan. In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicines . A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs, treatment with Accord Escitalopram and the serotonergic medicine should be discontinued immediately and symptomatic treatment initiated.

Akathisia/psychomotor restlessness

This is most likely to occur within the first few weeks of treatment. Increasing the dose in these patients may be detrimental.

Hyponatraemia

Caution should be exercised in patients at risk if Accord Escitalopram is used in combination with other medications which may cause hyponatraemia.

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.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8).

Coronary heart disease

Caution is advised in patients with coronary heart disease.

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 is started.

Angle-Closure Glaucoma

SSRIs including escitalopram 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. Accord Escitalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Accord Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3).

Suicide related behaviours (suicide attempt, suicidal thoughts as well as suicidal ideation and self-harm), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants including SSRIs such as Accord Escitalopram.

Withdrawal reactions:

Discontinuation symptoms upon stopping treatment are common, especially if discontinuation is abrupt (see section 4.8). The risk of developing these symptoms may depend on several factors, including the length of therapy, the dose and the rate of dose reduction. These symptoms usually occur within the first few days after treatment discontinuation, but there have been reports of discontinuation symptoms in patients who have missed a dose inadvertently. Generally these symptoms are self-limiting and usually resolve within 2 weeks, however, in some individuals they may continue for 2 to 3 months or longer. When stopping Accord Escitalopram, the dose should be gradually reduced over a period of one or two weeks in order to avoid possible withdrawal reactions (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Accord Escitalopram has a low potential for clinically significant medicine interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450, (CYP) 2C19, 3A4 and 2D6). Accord Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1 and 3A, and a weak inhibitor of 2D6.

Ritonavir: The pharmacokinetics of single doses of Accord Escitalopram was not changed by co-administration with a single dose of ritonavir (CYP3A4 inhibitor).

Ketoconazole: Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Cimetidine: Co-administration of racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) resulted in increased plasma concentrations of the racemate (43 % increase in AUC, 39 % increase in C_{max}). Thus, caution should be exercised at the upper end of the dose range of Accord Escitalopram when used concomitantly with high doses of cimetidine.

Monoamine oxidase inhibitors (MAOIs), sumatriptan and tramadol:

Co-administration with MAOIs (e.g moclobemide, linezolid) may cause serotonin syndrome. Accord

Escitalopram is contra-indicated in combination with non-selective, irreversible MAOIs. Accord Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing Accord Escitalopram treatment, before starting a non-selective, irreversible MAOI. Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects e.g. serotonin syndrome. There have been reports of enhanced effects when escitalopram has been given with lithium or tryptophan and therefore concomitant use of Accord Escitalopram with these medicines should be with caution (see section 4.4).

Selegiline: In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Racemic citalopram increased the AUC of selegiline by 29 %.

Desipramine: Co-administration with a single dose of desipramine (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of desipramine. Therefore, caution is advised when Accord Escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Metoprolol: Co-administration with a single dose of metoprolol 100 mg (a CYP2D6 substrate) resulted in a twofold increase in the C_{max} and a 52 % increase of the AUC of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and CR_{max} of pimozide. The coadministration of pimozide and citalopram resulted in a mean increase in the QTR_C interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Other: Pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline

(CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin. However, prothrombin time was slightly increased after a single dose of 25 mg warfarin. The International Normalised Ratio (INR) needs to be carefully monitored in patients on oral anticoagulant therapy when Accord Escitalopram is used concomitantly.

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when Accord Escitalopram 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.

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).

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding tendency (see section 4.4).

Medicines lowering the seizure threshold:

Accord Escitalopram may antagonise the activity of anti-epileptics by lowering 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), mefloquine, bupropion and tramadol.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Accord Escitalopram in pregnancy and lactation has not been established.

The following symptoms may occur in the neonate after maternal Accord Escitalopram use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs such as Accord Escitalopram in pregnancy, particularly in late pregnancy may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

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).

Breastfeeding

It is expected that escitalopram will be excreted into human milk.

Consequently, breastfeeding is not recommended during treatment with Accord Escitalopram.

Fertility

Animal data have shown that some SSRIs may affect sperm quality.

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

4.7 Effects on the ability to drive and use machines

The ability to drive and use machines may be impaired in patients treated with Accord Escitalopram due to somnolence, dizziness and drowsiness.

They should be warned of the possibility and advised to avoid such tasks if so affected. Accord Escitalopram does not impair intellectual function or psychomotor performance.

4.8 Undesirable effects

Adverse reactions observed with Accord Escitalopram are most frequent during the first one to two weeks of treatment and may decrease in intensity and frequency with continued treatment. After prolonged administration abrupt cessation of Accord Escitalopram may produce withdrawal reactions in some patients.

Tabulated list of adverse reactions

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia

Immune system disorders	Less frequent	Angiodema, anaphylactic reaction
Endocrine disorders	Less frequent	Inappropriate ADH secretion
Metabolism and nutrition disorders	Frequent	Decreased appetite, increased appetite, increased weight
	Less frequent	Hyponatraemia, decreased weight
Psychiatric disorders	Frequent	Insomnia, anxiety, restlessness, abnormal dreams, mania, mania, suicidal ideation, suicidal behaviour[1]. Female and male: libido decreased female: anorgasmia
	Less frequent	Bruxism, agitation, nervousness, panic attack, confusional state Aggression, depersonalisation, hallucination
Nervous system disorders	Frequent	Somnolence, dizziness, tremor.
	Less frequent	Sleep disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia and incoordination), headache, convulsion, drowsiness. Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia.
Eye disorders	Less frequent	Mydriasis, abnormal vision.
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia, Bradycardia
Vascular disorders	Less frequent	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Sinusitis, yawning
	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, constipation, dry mouth, dyspepsia
	Less frequent	Gastrointestinal bleeding, taste disturbance, anorexia.
Hepatobiliary disorders	Less frequent	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Frequent	Increased sweating
	Less frequent	rash, ecchymoses, pruritus, urticaria, alopecia, photosensitivity, purpura, angioedemas.
Musculoskeletal,	Frequent	Arthralgia, myalgia

connective tissue and bone disorders		
Renal and urinary disorders	Less Frequent	Urinary retention
Reproductive system and breast disorders	Frequent	Decreased libido (males and females), ejaculation disorder and impotence in males, abnormal orgasm in females.
	Less frequent	Galactorrhoea, anorgasmia, hyperprolactinaemia, metrorrhagia, postpartum haemorrhage[2] and menorrhagia in females. Male: priapism
General disorders and administrative site conditions	frequent	Fatigue, pyrexia
	Less frequent	Oedema
Investigations	Less frequent	Abnormal liver function tests.

[1] Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4).

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

Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease.

QT-prolongation may lead to ventricular dysrhythmia and torsade de pointes.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs. The mechanism leading to this risk is unknown.

Discontinuation symptoms seen when stopping treatment

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when Accord Escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

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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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 overdose

Symptoms: Doses of 190 mg have been taken without any symptoms being reported.

Treatment: There is no specific antidote to overdosage. Treatment is supportive and symptomatic. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradydysrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC-code: N 06 AB 10

Pharmacodynamics:

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake. Escitalopram has a minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors.

5.2 Pharmacokinetic properties

Absorption:

Absorption is independent of food intake (mean T_{max} is 4 hours after multiple dosing).

Distribution:

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 l/kg. The plasma protein binding of escitalopram is approximately 55 %.

Biotransformation:

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31 % and < 5 % of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination:

The elimination half-life ($t_{½\,\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0,6 l/min. Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine. Hepatic clearance is mainly by the P450 enzyme system. CYP2C19 is the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6. There is linear pharmacokinetics. Steady-state plasma levels are achieved in about 1 week. Average steady-state concentrations of 50 nmol/l (range 20 to 125 nmol/l) are achieved at a daily dose of 10 mg.

Elderly patients (> 65 years of age):

A longer half-life (about 50 %) and decreased clearance values, due to a reduced rate of metabolism, have been demonstrated in the elderly.

Reduced hepatic function:

Escitalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of escitalopram is twice as long in patients with hepatic impairment and steady-state escitalopram concentrations at a given dose will be approximately twice as high as in patients with normal liver function.

Reduced renal function:

Escitalopram is eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Polymorphism:

Based on *in vitro* results with escitalopram and *in vivo* results with the racemic citalopram, genetic polymorphism with respect to CYP2D6 is not known, with respect to CYP2C19, it may be of clinical relevance, as shown in limited numbers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Purified talc

Colloidal anhydrous silica

Magnesium stearate,

Microcrystalline cellulose,

Hypromellose E5,

Hypromellose (E-15)

Macrogol 400

Titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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Store in a cool, dry place at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Accord Escitalopram 10: Film-coated tablets are packed in either PVC/PE/PVdC-Alu, and/or Alu-Alu blister strips of 14 tablets per strip. 2 strips are packed in a unit carton as a pack size of 28.

Accord Escitalopram 20: Film-coated tablets are packed in either PVC/PE/PVdC-Alu, and/or Alu-Alu blister strips of 14 tablets per strip. 2 strips are packed in a unit carton as a pack size of 28.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park

6 Coombe Place

Rivonia

Gauteng

South Africa

8. REGISTRATION NUMBER

Accord Escitalopram 10: 44/1.2/0851

Accord Escitalopram 20: 44/1.2/0852

9. DATE OF FIRST AUTHORISATION

7 December 2012

10. DATE OF REVISION OF THE TEXT

05 February 2015