1.5.5.2 Clean Amended Proposed Professional Information

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BIO CITALOPRAM 10 film-coated tablets

BIO CITALOPRAM 20 film-coated tablets

BIO CITALOPRAM 30 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BIO CITALOPRAM 10: Each tablet contains citalopram hydrobromide equivalent to 10 mg citalopram.

BIO CITALOPRAM 20: Each tablet contains citalopram hydrobromide equivalent to 20 mg citalopram.

BIO CITALOPRAM 30: Each tablet contains citalopram hydrobromide equivalent to 30 mg citalopram.

Contains sugar (lactose monohydrate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

BIO CITALOPRAM 10: Round, biconvex, white coloured film-coated tablets, diameter 5,5 mm, with marking 10 on one side.

BIO CITALOPRAM 20: Oval, biconvex, scored, white coloured film-coated tablets, dimensions 8 x 5,5 mm, with marking 20 on one side.

BIO CITALOPRAM 30: Oval, biconvex, scored, white coloured film-coated tablets, dimensions 12,25 x 6 mm, with marking 30 on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BIO CITALOPRAM is indicated for the treatment of:

- Depression and prevention of relapse.
- Panic disorders with or without agoraphobia.
- Obsessive-compulsive disorder (OCD).

4.2 Posology and method of administration

Posology

Depression

20 mg a day as a single dose. Dosage may be increased by 20 mg a day at intervals of at least one week to a maximum of 40 mg depending on the patient's response.

Panic Disorder

10 mg a day as a single dose for the first week then increasing to 20 mg a day. The dose may be increased thereafter as required to a maximum of 40 mg a day depending on the patient's response.

Obsessive-Compulsive Disorder

20 mg a day as a single dose. This dose can be increased by 20 mg increments to a maximum of 40 mg a day depending on the patient's response.

Special populations:

Elderly: 10 to 20 mg a day as a single dose. The recommended maximum dose for the elderly is 20 mg daily.

Reduced hepatic function:

Mild or moderate hepatic impairment: An initial dose of 10 mg a day, as a single dose for two weeks is recommended. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Severe hepatic impairment: It is advised that patients are monitored continuously during dose titration, the maximum recommended dose is 20 mg daily.

Reduced renal function:

Dose adjustment is not necessary in cases of mild or moderate renal impairment.

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. BIO CITALOPRAM should be gradually withdrawn during a couple of weeks when stopping therapy see section 4.4).

BIO CITALOPRAM may be taken with or without food in the morning or evening.

4.3. Contraindications

- Hypersensitivity to citalopram or any of the ingredients in the formulation.
- Concurrent use with a monoamine oxidase inhibitor (MAOI), e.g. linezolid. At least 14 days should elapse between discontinuing the MAOI and initiating therapy with BIO CITALOPRAM. MAOIs should not be introduced for 7 days after discontinuation of BIO CITALOPRAM (see section 4.5).
- Severe renal impairment (creatinine clearance less than 20 ml/min).

- Safety and efficacy in pregnancy and lactation has not been established.
- Children under the age of 18 years (see section 4.4).
- BIO CITALOPRAM is contraindicated to use concurrently with medication known to prolong QT interval, e.g. pimozide (see section 4.5).
- BIO CITALOPRAM is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome. (see section 4.4).

4.4 Special warnings and precautions for use

BIO CITALOPRAM should be used with caution in:

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which BIO CITALOPRAM is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be

alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age

Safety and efficacy in children under 18 years of age have not been established. BIO CITALOPRAM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms.

In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Elderly patients

Caution should be used in the treatment of elderly patients. Longer half-life and decreased clearance due to a reduced rate of metabolism. A lower dose is recommended in the elderly (see section 4.2).

Reduced kidney and liver function

Caution should be used in the treatment of patients with reduced kidney and liver function.

Clearance of BIO CITALOPRAM is reduced. Cautious dosage titration and a lower maximum dose are recommended (see section 4.2).

Elimination is decreased. If creatinine clearance is less than 20 ml/min BIO CITALOPRAM should not be used (see section 4.3).

Paradoxical anxiety

Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect (see section 4.2).

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs 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 may be detrimental.

Mania

In patients with manic-depressive illness a change towards the manic phase may occur. BIO CITALOPRAM should be discontinued if the patient enters the manic phase.

Seizures

There is an increased risk of seizures. BIO CITALOPRAM should be discontinued in any patient who develops seizures or if there is an increase in seizure frequency. BIO CITALOPRAM should be used with

caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. Care is advised in patients receiving electroconvulsive therapy.

Diabetes

Rare occurrences of hypoglycaemia have been reported. In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Angle-closure Glaucoma

SSRIs including citalopram 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. BIO CITALOPRAM should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Serotonin syndrome

Serotonin syndrome is more likely to occur after an increase in dose. In rare cases, serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition (see section 4.5).
Treatment with BIO CITALOPRAM should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines

BIO CITALOPRAM should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan.

Haemorrhage

There have been reports of prolonged bleeding time and /or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleedings with SSRIs (see section 4.8). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly with concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of SSRIs and ECT; therefore caution is advisable.

Reversible, selective MAO-A inhibitors

BIO CITALOPRAM should not be used with monoamine oxidase inhibitors. For information on concomitant treatment with non-selective, irreversible MAO-inhibitors see section 4.5

St. John's wort

Undesirable effects may be more common during concomitant use of BIO CITALOPRAM and herbal preparations containing St John's wort (Hypericum perforatum). Therefore BIO CITALOPRAM and St John's wort preparations should not be taken concomitantly (see section 4.5).

Withdrawal symptoms seen on discontinuation of SSRI treatment

If therapy with BIO CITALOPRAM is to be discontinued, it is recommended that the dose is decreased gradually in order to prevent the possibility of a withdrawal syndrome.

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In a recurrence prevention clinical trial with BIO

CITALOPRAM, adverse events after discontinuation of active treatment were seen in 40 % patients versus 20 % in patients continuing BIO CITALOPRAM.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), 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 symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that BIO CITALOPRAM should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Psychosis

Treatment of psychotic patients with depressive episodes may increase psychotic symptoms.

Patients should be monitored during early therapy until improvement in depression is observed because suicide is an inherent risk in depressed patients.

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 BIO CITALOPRAM 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 emergence of suicidal impulses (see section 4.8) has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing BIO CITALOPRAM, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

QT interval prolongation

BIO CITALOPRAM may cause dose dependent QT interval prolongation and should not be prescribed at doses greater than 40 mg. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

Caution is advised in patients with pre-existing slow heart rates (bradycardia), or in patients with recent acute myocardial infarction or uncompensated heart failure.

Patients with congestive heart failure, bradydysrhythmia or predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicine use, are at risk of developing Torsade de Pointes.

To reduce the risk for dysrhythmias, electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with BIO CITALOPRAM is started.

An ECG (electrocardiogram) review is advised for patients with stable cardiac disease before treatment is started and also periodic ECG monitoring is recommended during treatment with BIO CITALOPRAM.

ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

If signs of cardiac arrhythmia occur during treatment with BIO CITALOPRAM, the treatment should be withdrawn and an ECG should be performed.

If the decision is made to discontinue treatment, BIO CITALOPRAM should be tapered (see section 4.2).

Excipients

BIO CITALOPRAM contains lactose monohydrate and persons that are lactose intolerant can experience bloating, flatulence and abdominal pain when taking BIO CITALOPRAM tablets.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take BIO CITALOPRAM.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

At the pharmacodynamic level cases of serotonin syndrome with citalopram and moclobemide and buspirone have been reported. Serotonin syndrome has developed after taking overdoses of moclobemide and BIO CITALOPRAM

Contraindicated combinations

MAO-Inhibitors

The simultaneous use of BIO CITALOPRAM and MAO-inhibitors can result in severe undesirable effects, including serotonin syndrome (see section 4.3).

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI, such as BIO CITALOPRAM, in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline and the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued an SSRI, such as BIO CITALOPRAM, and have been started on a MAOI

Some cases presented with features resembling serotonin syndrome. Symptoms of an active substance interaction with a MAOI include: agitation, tremor, myoclonus, and hyperthermia.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between BIO CITALOPRAM and other medicinal products that prolong the QT interval have not been performed. An additive effect of BIO CITALOPRAM and these medicinal products cannot be excluded.

Therefore, co-administration of BIO CITALOPRAM and other medicine that prolong the QT interval such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic BIO CITALOPRAM 40 mg/day for 11 days caused an increase in AUC and Cmax of pimozide, although not consistently throughout the study. The co-administration of pimozide and BIO CITALOPRAM resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of BIO CITALOPRAM and pimozide is contraindicated.

Combinations requiring precaution for use

Selegiline (selective MAO-B inhibitor)

A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered BIO CITALOPRAM (20 mg daily) and selegiline (10 mg daily) (a selective MAO B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of BIO CITALOPRAM and selegiline (in doses above 10 mg daily) is contraindicated.

Serotonergic medicinal products

Lithium and tryptophan

No pharmacodynamic interactions have been found in clinical studies in which BIO CITALOPRAM has been given concomitantly with lithium. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of BIO CITALOPRAM with these medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.

Increased risk of developing the serotonin syndrome, a rare but potentially fatal hyperserotonergic state.

Until further information is available, the simultaneous use of BIO CITALOPRAM and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

St. John's wort

Dynamic interactions between SSRIs and the herbal remedy St John's wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects (see section 4.4). Pharmacokinetic interactions have not been investigated.

Haemorrhage

Caution is warranted for patients who are being treated simultaneously with anticoagulants, medicinal products that affect the platelet function, such as non steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamole, and ticlopidine or other medicines (e.g. atypical antipsychotics) that can increase the risk of haemorrhage (see section 4.4).

ECT (electroconvusive therapy)

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and BIO CITALOPRAM (see section 4.4).

Alcohol

No pharmacodynamic or pharmacokinetic interactions have been demonstrated between BIO CITALOPRAM and alcohol.

However, the combination of BIO CITALOPRAM and alcohol is not advisable. The effects of alcohol may be increased.

Medicinal products inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia- / hypomagnesaemia-inducing medicinal products as these conditions increase the risk of malignant arrhythmias.

Medicinal products lowering the seizure threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants [SSRIs], neuroleptics [thioxanthenes and butyrophenones]), mefloquine, bupropion and tramadol).

Pharmacokinetic interactions

Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) isozymes of the cytochrome P450 system. The fact that citalopram is metabolised by more than one CYP means that inhibition of its biotransformation is less likely as inhibition of one enzyme may be compensated by another. Therefore co-administration of citalopram with other medicinal products in clinical practice has very low likelihood of producing pharmacokinetic medicinal product interactions.

Food

The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected by food.

Effect of other medicinal products on the pharmacokinetics of citalopram

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

A pharmacokinetic interaction study of lithium and citalopram did not reveal any pharmacokinetic interactions (see also above).

Cimetidine

Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of BIO CITALOPRAM. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be warranted. The AUC and the maximum plasma concentration of BIO CITALOPRAM are increased when BIO CITALOPRAM is administered concurrently with cimetidine

Co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of BIO CITALOPRAM may be necessary based on monitoring of side- effects during concomitant treatment (see section 4.4).

Metoprolol

Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram is co-administered with medicinal products 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 medicinal products 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 metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significant increase the effect of metoprolol on the blood pressure and cardiac rhythm.

Effects of citalopram on other medicinal products

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of BIO CITALOPRAM and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.

Levomepromazine, digoxin, carbamazepine

No change or only very small changes of clinical importance were observed when BIO CITALOPRAM was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9 (warfarin), CYP2C19 (imipramine and mephenytoin), CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxid) and triazolam).

No pharmacokinetic interaction was observed between BIO CITALOPRAM and levomepromazine, or digoxin, (indicating that citalopram neither induces nor inhibits P-glycoprotein).

Desipramine, imipramine

In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine was increased. When desipramine is combined with citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Published data on pregnant women (more than 2500 exposed outcomes) indicate no malformative foeto / neonatal toxicity, however, BIO CITALOPRAM should not be used during pregnancy.

Neonates should be observed if maternal use of BIO CITALOPRAM continues into the later stages of pregnancy, particular in the third trimester. Abrupt discontinuation should be avoided during pregnancy. The following symptoms may occur in the neonates after maternal SSRI/SNRI 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, and 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 in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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).

Breast-feeding

BIO CITALOPRAM is excreted into breast milk. It is estimated that the suckling infant will receive about 5 % of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child. Caution is recommended. If treatment with BIO CITALOPRAM is considered necessary, discontinuation of breast feeding should be considered.

Fertility

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

BIO CITALOPRAM has minor or moderate influence on the ability to drive and use machines. If affected these patients should not operate machinery or drive.

Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration due to the illness itself and psychoactive medicinal products can reduce the ability to make judgements and to react to emergencies. Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 Undesirable effects

Adverse effects observed with BIO CITALOPRAM are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently. The adverse reactions are presented at the MedDRA Preferred Term Level.

For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue.

Withdrawal reactions have been reported in association with selective serotonin inhibitors (SSRIs), including BIO CITALOPRAM. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with BIO CITALOPRAM should be avoided.

The majority of symptoms experienced on withdrawal of SSRIs, including BIO CITALOPRAM, are non-serious and self-limiting.

System organ class	Frequent	Less frequent	Frequency not known
Blood and lymphatic disorders			Thrombocytopenia
Immune system			Hypersensitivity,

disorders			anaphylactic reaction
Endocrine disorders			Inappropriate ADH secretion
Metabolism and nutrition disorders	Appetite decreased; weight decreased	Increased appetite, Weight increased, Hyponatraemia	Hypokalaemia
Psychiatric disorders	Sleep disorder, Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female), abnormal dreams, apathy.	Aggression, depersonalisation, hallucination, mania, libido increased, Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[1]	
Nervous system disorders	Somnolence, insomnia, headache, dizziness,-tremors, paraesthesia, disturbance in attention, migraine, amnesia	Syncope, dyskinesia, taste disturbance, convulsions grand mal,	Convulsions, serotonin syndrome extrapyramidal disorder, akathisia, movement disorder.
Eye disorders		Mydriasis (which may lead to acute narrow angle glaucoma), see section	Visual disturbance

		4.4 Special warnings and precautions for use	
Ear and labyrinth disorders	Tinnitus		
Cardiac disorders	Palpitations,	Bradycardia	QT-Prolongation, ventricular arrhythmia including Torsade de Pointes
Vascular disorders		Haemorrhage	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Yawning, rhinitis	Coughing	Epistaxis
Gastrointestinal disorders	Nausea, constipation, diarrhoea, dry mouth, vomiting, dyspepsia, abdominal pain, flatulence, salivary hypersecretion		Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepato-biliary disorders		Hepatitis	Liver function test abnormal
Skin and subcutaneous tissue disorders	Sweating increased, pruritus	Rash, urticaria, alopecia, purpura, photosensitivity	Ecchymosis, angioedemas

		reaction	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia		
Renal and urinary disorders	Urinary retention		
Reproductive system and breast disorders	Impotence, ejaculation disorder, ejaculation failure	Female: Menorrhagia.	Female: Metrorrhagia, postpartum haemorrhage Male: Priapism, galactorrhoea
General disorders and administrative site conditions	Asthenia, fatigue	Oedema	Pyrexia, malaise

[1] Cases of suicidal ideation and suicidal behaviours have been reported during citalopram 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 and 4.6).

Cases of QT-prolongation and ventricular arrhythmia including torsade de pointes have been reported during the postmarketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

Class effects

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

Withdrawal symptoms seen on discontinuation of SSRI treatment.

Discontinuation of BIO CITALOPRAM (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), 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 BIO CITALOPRAM treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Toxicity

Comprehensive clinical data on BIO CITALOPRAM overdose are limited and many cases involve concomitant overdoses of other drugs/alcohol. Fatal cases of BIO CITALOPRAM overdose have been reported with BIO CITALOPRAM alone; however, the majority of fatal cases have involved overdose with concomitant medications.

Fatal dose is not known. Patients have survived ingestion of more than 2 g BIO CITALOPRAM.

The effects may be potentiated by alcohol taken at the same time.

Potential interaction with TCAs, MAOIs and other SSRIs.

Symptoms

The following symptoms have been seen in reported overdose of BIO CITALOPRAM: convulsion, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, hyperpyrexia, and atrial and ventricular arrhythmia.

ECG changes including nodal rhythm, prolonged QT intervals and wide QRS complexes may occur. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported.

Rarely, features of the "serotonin syndrome" may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment

There is no known specific antidote to BIO CITALOPRAM.

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of ECG and vital signs until stable. ECG monitoring is advisable in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50 %.

Osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered.

If consciousness is impaired the patient should be intubated.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

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.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC code: N 06 AB 04

Mechanism of action

Citalopram is a bicyclic phthallane derivative with antidepressant effect. Biochemical and behavioural studies have shown that citalopram is a potent inhibition of specific serotonin (5-HT) reuptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

Citalopram, primarily through its (S)-enantiomer, blocks 5-HT reuptake, leading to potentiation of serotonergic activity in the central nervous system (CNS).

Citalopram is a very Selective Serotonin Reuptake Inhibitor (SSRI), with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

Citalopram also has little or no antidopaminergic, antiadrenergic, antiserotonergic, antihistaminergic or anticholinergic properties.

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series 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. A series of

functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity.

This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

Pharmacodynamic effects

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other SSRIs and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep.

Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

In humans citalopram does not impair cognitive (intellectual function) and psychomotor performance and has no or minimal sedative properties, either alone or in combination with alcohol.

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7.5 (90 % CI 5.9-9.1) msec at the 20 mg/day dose and 16.7 (90 % CI 15.0-18.4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Absorption

Absorption is almost complete and independent of food intake (T_{max} average / mean 3.8 hours). Oral bioavailability is about 80 %.

Distribution

The apparent volume of distribution $(V_d)_\beta$ is about 12.3 L/kg. The plasma protein binding is below 80 % for citalopram and its main metabolites. Time to reach steady state concentration is 1 to 2 weeks.

Biotransformation

Citalopram undergoes hepatic metabolism primarily involving the cytochrome P450 (CYP3A4) and 2C19 (CYP2C19) isoenzymes and to a small extent cytochrome P450 2D6 (CYP2D6) isoenzymes.
Citalopram is metabolized to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. The metabolites inhibit the reuptake of serotonin but are less potent that the parent molecule. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.

Elimination

Elimination half-life ($T_{½\beta}$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s) is about 0.33 L/min, and oral plasma clearance (Cl oral) is about 0.41 L/min.
Citalopram is excreted mainly via the liver (85 %) with the remainder (15 %) via the kidneys About 12 % of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min. Longer half-lives and decreased clearance due to a reduced rate of metabolism has been demonstrated in the elderly.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (≥ 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

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

Reduced renal function

Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Lactose monohydrate (18,19 %)

Croscarmellose sodium

Glycerin

Copolyvidone

Magnesium stearate

Microcrystalline cellulose

Opadry white

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of the container

BIO CITALOPRAM 10, 20 and 30 tablets are available in transparent PVC/PVdC/Aluminium blister packs of 30 tablets. Each blister strip contains 10 tablets and 3 blister strips are packed in an outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Block K West, Central Park

400, 16th Road, Halfway House

Midrand, 1685

8. REGISTRATION NUMBERS

BIO CITALOPRAM 10: 42/1.2/1009

BIO CITALOPRAM 20: 42/1.2/1010

BIO CITALOPRAM 30: 42/1.2/1067

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION

Registration Date: 25 November 2011.

10. DATE OF THE REVISION OF THE TEXT

31 March 2021 - SAHPRA approved 05 June 2021