## 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

**S5**

## 1. NAME OF THE MEDICINE

**CILIFT 20 mg TABLET**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of CILIFT 20 mg TABLET contains citalopram hydrobromide equivalent to 20 mg citalopram.

Contains sugar: Lactose monohydrate 75 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets

CILIFT 20 mg TABLET is a round, white to off-white, biconvex film-coated tablet, bisected on one side.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

CILIFT 20 mg TABLET is indicated for the treatment of:

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

### 4.2. Posology and method of administration

**Posology**

*Adults*

**Treating depression**

CILIFT 20 mg TABLET should be administered as a single oral dose of 20 mg (1 tablet) daily. Dependent on individual patient response, this may be increased to a maximum of 40 mg (two tablets) daily.

The dose may be taken in the morning or the evening, not necessarily with food.

*Duration of treatment*

The antidepressant effect usually sets in after 2 to 4 weeks. Treatment with CILIFT 20 mg TABLET is symptomatic and must therefore be continued for an appropriate length of time, usually up to 6 months after recovery in order to prevent relapse.

**Treating panic disorder**

A single dose of 10 mg (half a tablet) daily is recommended for the first week before

increasing the dose to 20 mg (1 tablet) daily. The dose may be further increased, up to a maximum of 40 mg (2 tablets) daily, dependent on individual patient response.

**Treating Obsessive Compulsive disorder (OCD)**

An initial dose of 20 mg (one tablet) is recommended. Dependent on individual patient response, the dose can be increased in increments of 20 mg (one tablet) to a maximum of 40 mg (two tablets) daily if necessary, based on clinical judgement.

*Duration of Treatment*

The onset of action in treating OCD is 2 to 4 weeks with further improvement over time.

***Special populations***

*Elderly patients (> 65 years) and patients with hepatic impairment*

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 10 mg to 20 mg daily.

Depending on individual patient response. The recommended maximum dose is 20 mg (one tablet) daily.

*Reduced hepatic function*

Dosage should be halved.

An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function.

*Reduced renal function*

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

CILIFT 20 mg TABLET is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see section 4.3 and section 5.2).

*Poor metabolisers of CYP2C19*

An initial dose of 10 mg daily during the first two weeks of treatment is recommended for patients who are known to be poor metabolisers with respect to CYP2C19. The dose may be increased to a maximum of 20 mg daily depending on individual patient response.

*Withdrawal symptoms seen on discontinuation of CILIFT 20 mg TABLET*

Abrupt discontinuation of CILIFT 20 mg TABLET should be avoided. When stopping treatment with CILIFT 20 mg TABLET the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate (see section 4.8 and section 4.4).

**Paediatric population**

*Children and adolescents ( < 18 years of age)*

CILIFT 20 mg TABLET should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3 and section 4.4).

**Method of administration**

For oral administration.

CILIFT 20 mg TABLET is administered as a single daily dose. CILIFT 20 mg TABLET can be taken at any time of the day without regard to food intake.

### 4.3. Contraindications

CILIFT 20 mg TABLET is contraindicated in:

- Patients with hypersensitivity to citalopram or to any excipients in CILIFT 20 mg TABLET (see section 6.1).
- Severely impaired renal function (creatinine clearance of less than 30 ml/min) (see section 5.2).
- Children and adolescents under the age of 18 years (see section 4.4 and section 4.8).
- Combination with monoamine oxidase inhibitors (MAOIs):

  Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI, such as citalopram, as in CILIFT 20 mg TABLET, in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAO-B inhibitor selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

  Some cases presented with features resembling serotonin syndrome.

  CILIFT 20 mg TABLET must not be used in combination with a MAOI, including selegiline in doses above 10 mg daily.

  Treatment with CILIFT 20 mg TABLET may be instituted 14 days after discontinuation of non-selective MAOIs and minimum of one day after discontinuation of moclobemide.

  Treatment with MAOIs may be introduced 7 days after discontinuing CILIFT 20 mg TABLET (see section 4.5).
- Patients with known QT interval prolongation or congenital long QT syndrome (see section 4.4, section 4.8 and section 5.1).

- Combination with medicines that are known to prolong the QT interval (see section 4.4 and section 4.5).
- Combination with linezolid (see section 4.5).
- Concomitant treatment with pimozide (see section 4.5).

## 4.4. Special warnings and precautions for use

*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.

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, such as CILIFT 20 mg TABLET. This risk may persist until significant remission occurs. A causal role however, for antidepressant medicine, such as CILIFT 20 mg TABLET, in inducing such behaviour, has not been established.

Patients being treated with CILIFT 20 mg TABLET 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.

Other psychiatric conditions for which CILIFT 20 mg TABLET is prescribed can also be associated with an increased risk of suicide related events.

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 CILIFT 20 mg TABLET, 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 CILIFT 20 mg TABLET, 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, CILIFT 20 mg TABLET should be tapered (see section 4.4 and section 4.8).

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 medicines, such as CILIFT 20 mg TABLET, 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 medicine 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.

*Withdrawal symptoms seen on discontinuation of CILIFT 20 mg TABLET*

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. After prolonged administration, abrupt cessation of CILIFT 20 mg TABLET may produce withdrawal symptoms such 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 in some patients. These symptoms are not indicative of addiction.

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 this was also reported 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 to 3 months or more). It is therefore advised that the dosage of CILIFT 20 mg TABLET should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs to avoid occurrence of discontinuation symptoms (see section 4.2).

*ECT (electroconvulsive therapy)*

There is little clinical experience of concurrent use of CILIFT 20 mg TABLET and electro-convulsive treatment, therefore caution is advisable.

*Mania*

In patients with manic-depressive illness, a change towards the manic phase may occur. Should the patient enter a manic phase CILIFT 20 mg TABLET should be discontinued.

*QT interval prolongation*

CILIFT 20 mg TABLET has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia 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 interval prolongation or other cardiac diseases (see section 4.3, section 4.5, section 4.8, section 4.9 and section 5.1).

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 CILIFT 20 mg TABLET is started.

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

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 dysrhythmia occur during treatment with CILIFT 20 mg TABLET, the treatment should be withdrawn and an ECG should be performed.

*Elderly patients*

Caution should be used in the treatment of elderly patients (see section 4.2).

*Reduced kidney and liver function*

Caution should be used in the treatment of patients with reduced kidney and liver function (see section 4.2).

*Paradoxical anxiety*

Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants, such as CILIFT 20 mg TABLET. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose of CILIFT 20 mg TABLET 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 an adverse reaction with the use of SSRIs, such as CILIFT 20 mg TABLET (see section 4.8). Hyponatraemia generally reverses on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.

*Akathisia or psychomotor restlessness*

The use of CILIFT 20 mg TABLET 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.

*Seizures*

Seizures are a potential risk with antidepressant medicines, such as CILIFT 20 mg TABLET. CILIFT 20 mg TABLET should be discontinued in any patient who develops seizures. CILIFT 20 mg TABLET should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. CILIFT 20 mg TABLET should be discontinued if there is an increase in seizure frequency.

*Diabetes*

In patients with diabetes, treatment with an SSRI, such as CILIFT 20 mg TABLET, can alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

*Glaucoma*

SSRIs, including CILIFT 20 mg TABLET, 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. CILIFT 20 mg TABLET should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

*Serotonin syndrome*

Serotonin syndrome has been reported in patients using SSRIs, such as CILIFT 20 mg TABLET. A combination of symptoms such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition (see section 4.5). Treatment with CILIFT 20 mg TABLET should be discontinued immediately and symptomatic treatment initiated.

*Serotonergic medicines*

CILIFT 20 mg TABLET should not be used concomitantly with medicines with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan (see section 4.5).

Concomitant administration of citalopram, as in CILIFT 20 mg TABLET, and buprenorphine may result in serotonin syndrome, a potentially life-threatening syndrome (see section 4.5). If concomitant treatment with buprenorphine is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

*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, such as CILIFT 20 mg TABLET (see section 4.8). Caution

is advised in patients taking CILIFT 20 mg TABLET, particularly with concomitant use of active medicines known to affect platelet function or other active medicines that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

SSRIs/SNRIs, such as CILIFT 20 mg TABLET, may increase the risk of postpartum haemorrhage (see section 4.6 and section 4.8).

*Reversible, selective MAO-A inhibitors*

The combination of CILIFT 20 mg TABLET with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome (see section 4.5). For information on concomitant treatment with non-selective, irreversible MAO-inhibitors, see section 4.3 and section 4.5.

*St. John's wort*

Undesirable effects may be more common during concomitant use of CILIFT 20 mg TABLET and herbal preparations containing St. John's wort (*Hypericum perforatum*).

Therefore CILIFT 20 mg TABLET and St. John's wort preparations should not be taken concomitantly (see section 4.5).

*Sexual dysfunction*

SSRIs/SNRIs, such as CILIFT 20 mg TABLET, 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, such as CILIFT 20 mg TABLET.

*Risk of parasomnias*

SSRIs, such as citalopram, as in CILIFT 20 mg TABLET, may cause various parasomnias. Parasomnia is an umbrella term for complex movements or behaviours during sleep, including abnormal dreaming, nightmares (paroniria) and sleepwalking (somnambulism). The most frequently reported terms are abnormal dreams, paroniria and sleep disorder.

*Psychosis*

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

**Paediatric population**

*Use in children and adolescents under 18 years of age*

CILIFT 20 mg TABLET 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 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, such as CILIFT 20 mg TABLET, compared to those treated with placebo.

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

*Excipients*

CILIFT 20 mg TABLET contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take CILIFT 20 mg TABLET.

## 4.5. Interaction with other medicines and other forms of interaction

**Pharmacodynamic interactions**

At the pharmacodynamic level cases of serotonin syndrome with CILIFT 20 mg TABLET and moclobemide and buspirone have been reported.

**Contraindicated combinations**

*MAO-Inhibitors*

The simultaneous use of CILIFT 20 mg TABLET and MAO-inhibitors can result in severe undesirable effects, including serotonin syndrome (see section 4.3 and 4.4). Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI, such as CILIFT 20 mg TABLET, in combination with a MAOI, including the irreversible MAOI selegiline and the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of an active

medicine interaction with a MAOI include: tremor, myoclonus hyperthermia, rigidity, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma (see section 4.3).

*QT interval prolongation*

Pharmacokinetic and pharmacodynamic studies of citalopram, as in CILIFT 20 mg TABLET, combined with other medicines that prolong the QT interval have not been performed. An additive effect of citalopram and these medicines cannot be excluded. Therefore, co-administration of CILIFT 20 mg TABLET with medicines that prolong the QT interval, such as Class IA and III antidysrhythmics (e.g. amiodarone, quinidine), antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine) and anti-retrovirals (e.g. ritonavir, saquinavir, lopinavir), is contraindicated (see section 4.3).

*Pimozide*

Co-administration of a single dose of pimozide 2 mg to patients treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and $C_{max}$ of pimozide, although not consistently throughout the study. The co-administration of pimozide and CILIFT 20 mg TABLET 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 citalopram, as in CILIFT 20 mg TABLET, and pimozide is contraindicated (see section 4.3).

**Combinations requiring precaution for use**

*Selegiline (selective MAO-B inhibitor)*

A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily), as in CILIFT 20 mg TABLET, and selegiline (10 mg daily) (a selective MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of CILIFT 20 mg TABLET and selegiline (in doses above 10 mg daily) is contraindicated (see section 4.3).

*Serotonergic medicines*

No pharmacodynamic interactions have been found in clinical studies in which citalopram, as in CILIFT 20 mg TABLET, has been given concomitantly with lithium. However, there may be enhanced effects when SSRIs, including CILIFT 20 mg TABLET, are given with lithium, sumatriptan or tryptophan. Therefore, the concomitant use of CILIFT 20 mg TABLET with these medicines should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

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

Until further information is available. The simultaneous use of CILIFT 20 mg TABLET and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

Buprenorphine

Citalopram, as in CILIFT 20 mg TABLET, should be used cautiously when co-administered with buprenorphine, as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

*Medicines lowering the seizure threshold*

CILIFT 20 mg TABLET can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, other SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).

*St. John's wort*

Pharmacodynamic interactions between CILIFT 20 mg TABLET and the herbal remedy St. John's wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects (see section 4.4 and section 4.8). Pharmacokinetic interactions have not been investigated.

*Haemorrhage*

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

*ECT (electroconvulsive therapy)*

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram, as in CILIFT 20 mg TABLET (see section 4.4).

*Alcohol*

No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram, as in CILIFT 20 mg TABLET, and alcohol. However, the combination of CILIFT 20 mg TABLET and alcohol is not advisable.

*Medicines inducing hypokalaemia/hypomagnesaemia*

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

*Desipramine, imipramine*

In a pharmacokinetic study no effect was demonstrated on either CILIFT 20 mg TABLET or imipramine levels, although the level of desipramine, the primary metabolite of imipramine was increased. When desipramine is combined with CILIFT 20 mg TABLET, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

*Neuroleptics*

Experience with CILIFT 20 mg TABLET has not revealed any clinically relevant interactions with neuroleptics. However, the possibility of a pharmacodynamic interaction cannot be excluded.

**Pharmacokinetic interactions**

Biotransformation of citalopram, as in CILIFT 20 mg TABLET, to demethylcitalopram is mediated by CYP2C19 (approximately 38 %), CYP3A4 (approximately 31 %) and CYP2D6 (approximately 31 %) isozymes of the cytochrome P450 system. The fact that CILIFT 20 mg TABLET 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 CILIFT 20 mg TABLET with other medicines in clinical practice has very low likelihood of producing pharmacokinetic medicines interactions.

*Food*

The absorption and other pharmacokinetic properties of CILIFT 20 mg TABLET have not been reported to be affected by food.

**Effect of other medicines on the pharmacokinetics of CILIFT 20 mg TABLET**

Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of citalopram, as in CILIFT 20 mg TABLET.

A pharmacokinetic interaction study of lithium and citalopram, as in CILIFT 20 mg TABLET, did not reveal any pharmacokinetic interactions.

*Cimetidine*

Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram, as in CILIFT 20 mg TABLET. Caution is advised when administering CILIFT 20 mg TABLET in combination with cimetidine. Dose adjustment may be warranted.

Co-administration of escitalopram (the active enantiomer of citalopram, as in CILIFT 20 mg TABLET) 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 CILIFT 20 mg TABLET may be necessary based on monitoring of undesirable effects during concomitant treatment (see section 4.4).

*Metoprolol*

Escitalopram (the active enantiomer of citalopram, as in CILIFT 20 mg TABLET) is an inhibitor of the enzyme CYP2D6. Caution is recommended when CILIFT 20 mg TABLET 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.

*Effects of CILIFT 20 mg TABLET on other medicines*

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram, as in CILIFT 20 mg TABLET, 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. Caution is recommended when metoprolol and citalopram, as in CILIFT 20 mg TABLET, are co-administered.

Citalopram, as in CILIFT 20 mg TABLET, 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 citalopram, as in CILIFT 20 mg TABLET, 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 epoxide) and triazolam).

No pharmacokinetic interaction was observed between citalopram, as in CILIFT 20 mg TABLET, and levomepromazine, or digoxin, (indicating that citalopram neither induces nor inhibits P-glycoprotein).

## 4.6. Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

**Pregnancy**

Data on pregnant women (more than 2 500 exposed outcomes) indicate no malformative foeto / neonatal toxicity, however CILIFT 20 mg TABLET should not be used during pregnancy.

Neonates should be observed if maternal use of CILIFT 20 mg TABLET 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 CILIFT 20 mg TABLET 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.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI, such as citalopram as in CILIFT 20 mg TABLET, exposure within the month prior to birth (see section 4.4 and section 4.8).

Epidemiological data have suggested that the use of SSRIs, such as citalopram, as in CILIFT 20 mg TABLET, 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 1 000 pregnancies. In the general population 1 to 2 cases of PPHN per 1 000 pregnancies occur.

**Breastfeeding**

CILIFT 20 mg TABLET is excreted into breast milk. Mothers breastfeeding their infants should not be treated with CILIFT 20 mg TABLET.

**Fertility**

Animal data have shown that citalopram, as in CILIFT 20 mg TABLET, may affect sperm quality.

Human case reports with some SSRIs, such as citalopram, as in CILIFT 20 mg TABLET, have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

## 4.7. Effects on ability to drive and use machines

CILIFT 20 mg TABLET has minor influence on the ability to drive and use machines.

Since adverse reactions such as dizziness, drowsiness and amnesia have been reported in patients taking CILIFT 20 mg TABLET, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CILIFT 20 mg TABLET does not adversely affect their ability to do so (see section 4.8).

## 4.8. Undesirable effects

*a) Summary of the safety profile*

Undesirable effects observed with citalopram, as in CILIFT 20 mg TABLET, are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

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

*b) Tabulated list of adverse reactions*

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | Thrombocytopenia | |
| **Immune system disorders** | | Hypersensitivity, anaphylactic reaction | |
| **Endocrine disorders** | | Inappropriate ADH secretion | |
| **Metabolism and nutrition disorders** | Weight loss, weight gain, decreased appetite | Hyponatraemia (particularly in the elderly), appetite increased | Hypokalaemia |
| **Psychiatric disorders** | Anxiety, decreased libido, agitation, nervousness, confusional state, abnormal orgasm (female), abnormal dreams, sleep disorder, apathy. | Mania, aggression, depersonalisation, hallucination, panic attack, bruxism, restlessness, increased libido, suicidal ideation, suicidal behaviour[2], in children: hostility, suicidal ideation, self-harm | Parasomnia |
| **Nervous system disorders** | Insomnia, somnolence, drowsiness, paraesthesia, headache, tremor, dizziness, disturbance in attention, migraine, amnesia | Convulsions, convulsion grand mal, extrapyramidal side effects, confusion, syncope, serotonin syndrome, akathisia, dyskinesia movement disorder, taste disturbance | |
| **Eye disorders** | Accommodation disturbances | Mydriasis (which may lead to acute narrow angle glaucoma) | Visual disturbance |

| | | | |
|---|---|---|---|
| **Ear and labyrinth disorders** | Tinnitus | | |
| **Cardiac disorders** | Decrease in pulse rate, bradycardia, tachycardia, palpitations | Electrocardiogram QT prolongation[1], ventricular dysrhythmia including torsade de pointes | |
| **Vascular disorders** | | Haemorrhage, orthostatic hypotension | |
| **Respiratory, thoracic and mediastinal disorders** | Yawning, rhinitis | Nasal congestion, epistaxis, coughing | |
| **Gastrointestinal disorders** | Dry mouth, nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain, flatulence, increased salivation | Gastrointestinal haemorrhage including rectal haemorrhage) | |
| **Hepatobiliary disorders** | | Hepatitis, abnormal liver function test | |
| **Skin and subcutaneous tissue disorders** | Increased sweating, pruritis | Rash, urticaria, alopecia, purpura, photosensitivity reaction, ecchymosis, angioedema | |
| **Musculoskeletal and connective tissue disorders** | Myalgia, arthralgia | | |
| **Renal and urinary disorders** | Micturition disorder | Urinary retention | |
| **Reproductive system and breast disorders** | Ejaculation disorder, impotence, ejaculation failure | Menorrhagia, metrorrhagia, priapism, galactorrhoea | Postpartum haemorrhage* |
| **General disorders and administrative site conditions** | Fatigue, asthenia | Pyrexia, oedema, malaise | Neuroleptic malignant syndrome |

[1] Cases of QT-prolongation and ventricular dysrhythmia 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 section 4.3, section 4.4, section 4.5, section 4.9 and section 5.1).

[2] Cases of suicidal ideation and suicidal behaviours have been reported during citalopram, as in CILIFT 20 mg TABLET, therapy or early after treatment discontinuation (see section 4.4).

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

*c) Description of selected adverse reactions*

*Bone fractures*

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs, such as CILIFT 20 mg TABLET, and TCAs. The mechanism leading to this risk is unknown.

*Withdrawal symptoms seen on discontinuation*

Discontinuation of CILIFT 20 mg TABLET (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 CILIFT 20 mg TABLET treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 4.4).

*d) Paediatric population*

*Children and adolescents under 18 years of age*

In children reports of hostility and suicidal ideation (see section 4.3 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:** https://www.sahpra.org.za/health-products-vigilance/

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088/ +27 (0)11 239-6200

## 4.9. Overdose

**Symptoms**

The fatal dose is not known. Patients have survived ingestion of up to 2 g citalopram, as in CILIFT 20 mg TABLET. The effects will be potentiated by alcohol taken at the same time. Potential interactions with tricyclic antidepressants and MAOIs (see section 4.5). Comprehensive clinical data on citalopram, as in CILIFT 20 mg TABLET, overdose are limited, and many cases involve concomitant overdoses of other medicines/alcohol. Fatal cases of citalopram, as in CILIFT 20 mg TABLET, overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medicines/alcohol.

The following symptoms have been seen in reported overdose of CILIFT 20 mg TABLET: tiredness, weakness, sedation, convulsion, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, drowsiness, torsade de pointes, stupor, dystonia, sweating, cyanosis, hyperventilation, hyperpyrexia, nodal rhythm, and atrial and ventricular dysrhythmia.

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. 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 has been reported.

**Treatment**

There is no known specific antidote to citalopram, as in CILIFT 20 mg TABLET.

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac, ECG and vital signs until stable. ECG monitoring is advisable in all cases of overdose especially in patients with congestive heart failure/ bradydysrhythmias, in patients using concomitant medicines that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment. An ECG should be taken. Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal given half an hour (½) hour after ingestion of citalopram, as in CILIFT 20 mg TABLET, 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.

Medical surveillance for about 24 hours is advisable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Category and Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

ATC code: N06AB04

*Mechanism of action*

Citalopram, a bicyclic phthalane derivative, is a selective serotonin reuptake inhibitor (SSRI). It has an antidepressant effect. The medicine is a racemate, in which one of the enantiomers is responsible for the effect. The pharmacodynamic effect is specifically related to a selective

inhibition of serotonin (5-HT) uptake. It has no effect on the uptake of noradrenaline, dopamine or GABA.

Moreover neither citalopram nor its metabolites have antidopaminergic, antiadrenergic, antiserotoninergic, antihistaminergic or anticholinergic (antimuscarinic) properties. After prolonged treatment, the 5-HT- uptake inhibitory efficacy is unchanged and citalopram does not induce changes in the density of neurotransmitter receptors at the recommended dosages.

In a double-blind, placebo-controlled ECG study in healthy patients, the change from baseline in QTc (Fridericia-correction) was 7,5 (90 % CI 5,9 to 9,1) ms at the 20 mg/day dose and 16,7 (90 % CI 15,0 to 18,4) ms at the 60 mg day/dose (see section 4.3, section 4.4, section 4.5, section 4.8 and section 4.9).

Prevention of the reuptake of the monoamine transmitter serotonin potentiates the action in the brain, which appears to be associated with antidepressant activity.

## 5.2. Pharmacokinetic properties

**Absorption**

Citalopram is readily absorbed from the gastrointestinal tract and oral bioavailability is high (> 80 %), maximum plasma concentrations are reached within 4 hours (interval 1 to 6 hours) after oral administration.

**Distribution**

Citalopram is widely distributed throughout the body (the volume of distribution is ± 14 litres per kg).

A linear relationship has been demonstrated between steady-state plasma levels and

administered dose and varies four-fold between individuals treated with the same dose.

Steady state levels are obtained within 1 to 2 weeks. Protein binding is about 80 %.

**Biotransformation**

Citalopram is metabolised by demethylation, deamination and oxidation to inactive metabolites.

Unchanged citalopram is a predominant compound in plasma. The metabolites have the same pharmacological effect as citalopram, but are less potent. It is not known whether the kinetics of the active enantiomer differs in patients, who are slow metabolisers of sparteine/debrisoquine or mephenytoin.

**Elimination**

The elimination half-life of citalopram is reported to be about 36 hours (interval 28 to 42 hours)

The systemic plasma clearance is about 0,4 L/min.

Longer half-lives and decreased clearance value due to a reduced rate of metabolism have been demonstrated in elderly patients, and therefore these patients should be given a lower dose.

Patients with reduced liver function have a slower elimination.

Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min) (see section 4.2 and section 4.3).

It is excreted in the urine and faeces.

The excretion proceeds with the urine. In steady-state about 30 % of the administered dose

is identified in the urine, 12 % as unchanged medicine.

Citalopram is a weak inhibitor of the cytochrome P450 IID6 metabolic pathway with a consequent reduction in potential for adverse events and interactions.

Citalopram is distributed into breast milk in very low concentrations.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, methocel, polyethylene glycol 400, purified talc, starch maize, starch maize (pregelatinised), titanium dioxide (C.I. no. 77891).

### 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 moisture.

Keep the blisters in the carton until required for use.

### 6.5. Nature and contents of container

Blister packs of 30 and 90 tablets packed in red, transparent polyvinyl chloride or polyvinylidine chloride blisters with silver tempered aluminium foil with a leaflet in each pre-printed carton.

Blister packs of 30 and 90 tablets packed in clear, rigid, polyvinyl chloride, laminated with polyethylene and coated with polyvinylidine chloride with silver tempered aluminium foil with a leaflet in each pre-printed carton.

Metallised lay flat bankbags of 28 tablets each sealed on the top with a lay-flat zip.

Not all packs and pack sizes are necessarily marketed.

### 6.6. Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

## 8. REGISTRATION NUMBER

36/1.2/0092

## 9. DATE OF FIRST AUTHORISATION

07 March 2003

## 10. DATE OF REVISION OF TEXT

24 May 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Namibia: NS3 04/1.2/1727

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