SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Citalopram STADA 10 mg filmomhulde tabletten
Citalopram STADA 20 mg filmomhulde tabletten
Citalopram STADA 40 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Citalopram STADA 10 mg film-coated tablet
Each film-coated tablet contains 12.495 mg citalopram hydrobromide, equivalent to 10 mg citalopram.
Citalopram STADA 20 mg film-coated tablet
Each film-coated tablet contains 24.99 mg citalopram hydrobromide, equivalent to 20 mg citalopram.
Citalopram STADA 40 mg film-coated tablet
Each film-coated tablet contains 49.98 mg citalopram hydrobromide, equivalent to 40 mg citalopram.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

Citalopram STADA 10 mg film-coated tablet
Round, white tablets with a diameter of 6 mm.
Citalopram STADA 20 mg film-coated tablet
Round, white tablets with a break-line and diameter of 8 mm.
The tablets can be divided into equal doses.
Citalopram STADA 40 mg film-coated tablet
Round, white tablets with a break-line and diameter of 10 mm.
The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

4.2 Posology and method of administration

Posology

Adults
Citalopram should be administered as a single oral dose of 20 mg daily.
Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily.
Special populations

Elderly patients (> 65 years of age)

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 10-20 mg per day. The recommended maximum dose for older people is 20 mg daily.

Renal impairment
Dosage adjustment is not required if the patient has mild to moderate renal impairment. Caution is advised in patients with severe renal impairment (creatinine clearance less than 30 ml/min, see section 5.2).

Hepatic impairment
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 (see section 5.2).

Poor metabolisers regarding 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, (see section 5.2).

Paediatric population
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Withdrawal symptoms seen on discontinuation
Abrupt discontinuation should be avoided. When stopping treatment with Citalopram 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 (see section 4.4 and section 4.8). If intolerable symptoms occur following a decrease in the dose upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

Citalopram should be administered as a single oral dose, either in the morning or in the evening. The tablets can be taken with or without food, but with fluid.

Duration of treatment

Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. Treatment should continue until the patient has been free of symptoms for 4-6 months. Citalopram should be withdrawn slowly, it is advised that the dose is gradually reduced over 1-2 week periods.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- MAOIs (monoamine oxidase inhibitors)
  Some cases presented with features resembling serotonin syndrome.
- citalopram should not be given to patients receiving Monoamine Oxidase Inhibitors (MAOIs) including selegiline in daily doses exceeding 10 mg/day. Citalopram should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after dis-continuation of a reversible MAOI (RIMA) as stated in the prescribing text of the RIMA. MAOIs should not be introduced for seven days after discontinuation of citalopram (see section 4.5)
- citalopram is contraindicated in the combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5)

- concomitant treatment with pimozide (see section 4.5)
- citalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome
- citalopram is contraindicated together with medicinal products that are known to prolong the QT-interval (see section 4.5)

4.4 Special warning and precautions for use

Treatment of elderly patients and patients with reduced kidney and liver function, see section 4.2.

Paediatric population
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.

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.

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 reverse on discontinuation of therapy. Older female patients seem to be at particularly high risk.

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 stage of recovery.

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.

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 ac-companied 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
Citalopram should be used with caution in patients with a history of mania/hypomania. Citalopram should be discontinued in any patient entering a manic phase.

Seizures
Seizures are a potential risk with antidepressant drugs.
Citalopram should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

Diabetes
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. Citalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Serotonin syndrome
In rare cases a 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. Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines
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 ecchymosis, gynaecological haemorrhages, gastrointestinal bleedings 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 in concomitant use with 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).

Electroconvulsive Therapy (ECT)
There is little clinical experience of concurrent administration of citalopram and electro-convulsive therapy, therefore caution is advisable.

Reversible, selective MAO A inhibitors
The combination of citalopram 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 4.5.

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

Withdrawal symptoms seen on discontinuation
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. Dizziness, sensory disturbances (including paraesthesia, sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported re-actions. 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 Citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation", section 4.2)."

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

QT interval prolongation
Citalopram has been found to cause a dose-dependent prolongation of the QT-interval. 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 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 arrhythmias and should be corrected before treatment with citalopram is started.

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

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

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.

Renal impairment
The use of citalopram in patients with severe renal impairment (creatinine clearance less than 30 ml/min.) is not recommended as no information is available on use in these patients (see section 4.2).

Hepatic impairment
In cases of impaired hepatic function dose reduction is recommended (see section 4.2) and liver function has to be closely monitored.

Dose titration
At the beginning of the treatment, insomnia and agitation can occur. A dose titration may be

helpful.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
At the pharmacodynamic level cases of serotonin syndrome with citalopram and moclobemide and buspirone have been reported.

Contraindicated combinations

MAO-inhibitors
The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including the serotonin syndrome (see section 4.3).
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI 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 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: hyperthermia, rigidity, myoclonus, 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 between citalopram and other medicinal products that prolong the QT interval have not been performed. An additive effect of citalopram and these medicinal products cannot be excluded. Therefore, co-administration of citalopram with medicinal products 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-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.
Accordingly, caution is warranted for hypokalaemia/hypomagnesaemia inducing drugs as they, like citalopram, also potentially prolong the QT interval.

Pimozide
Concomitant administration of a single dose of 2 mg pimozide to healthy volunteers, who were treated with citalopram 40 mg/day for 11 days, caused only a minor increase in the AUC and C_{max} of pimozide of approximately 10 %, not being statistically significant. Despite the minor increase in plasma pimozide levels, the QTc interval was more prolonged after concomitant administration of citalopram and pimozide (on average 10 ms) as compared to administration of a single dose of pimozide alone (on average 2 ms). Since this interaction was already observed after administration of a single dose of pimozide, concomitant treatment with citalopram and pimozide is contraindicated.

Combinations requiring precaution for use

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

Serotonergic medicinal products
Lithium and tryptophan
There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic effects when SSRIs were administered in combination with lithium or tryptophan. Caution is advised during simultaneous use of

citalopram with these active substances. 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.
Until further information is available, the simultaneous use of 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 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 function of thrombocytes, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamole, and ticlopidine or other medicines (e.g. atypical antipsychotics, phenothiazines, tricyclic depressants) 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 electro-convulsive therapy (ECT) and citalopram (see section 4.4).

Alcohol
No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram and alcohol. However, the combination of citalopram and alcohol is not advisable.

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 (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).

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.

Neuroleptics
Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction can-not be excluded.

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.

Influence 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 citalopram. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.

Co-administration of escitalopram 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 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 escitalopram 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 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 desmethylcitalopram 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
Thus no change or only very small changes of no clinical importance were observed when 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 epoxide) and triazolam).

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit P-glycoprotein).

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 2,500 exposed outcomes) indicates no malformative foeto/ neonatal toxicity. Citalopram can be used during pregnancy if clinically needed, taking into account the aspects mentioned below.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular 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.

Cases of withdrawal symptoms in the newborn child have been described after the use of SSRI at the end of pregnancy. Neonates should be observed if maternal use of citalopram continues into the later stages of pregnancy particular in the third trimester.
Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may also occur in the neonate 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, 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 exposure within the month prior to birth (see sections 4.4, 4.8).

Breast-feeding
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.

Fertility
Animal data have shown that citalopram may affect sperm quality (see section 5.3).
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 ability to drive and use machines

Citalopram has minor or moderate influence on the ability to drive and use machines.
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 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.

The table shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either ≥ 1 % of patients in double-blind placebo-controlled trials or in the

post-marketing period. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available data).

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders						Thrombocytopenia.
Immune system disorders			Allergic reactions.		Anaphylactic reactions.	Hypersensitivity.
Endocrine disorders				The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported, predominantly in older people (see section 4.4).		
Metabolism and nutrition disorders		Weight decrease, weight increase, appetite decreased, increased appetite, anorexia.		Hyponatraemia has been reported, predominantly in older people (see section 4.4).		Hypokalaemia.
Psychiatric disorders	Agitation, nervousness.	Sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, apathy, confusional state, abnormal orgasm (female).	Euphoria, increased libido, aggression, depersonalisation, hallucination, mania.		Panic attacks (these symptoms may be due to the underlying disease).	Suicidal ideation and suicidal behaviours *, bruxism, restlessness.
Nervous system disorders	Somnolence, insomnia, headache, tremor, dizziness.	Migraine, taste abnormalities, paraesthesia, disturbance in attention.	Extrapyramidal disorders, convulsions, syncope.	Serotonin syndrome has been reported in patients using SSRIs, convulsion grand mal.		Psychomotor restlessness/akathisia (see section 4.4), movement disorder.
Eye disorders	Abnormal accommodation.	Abnormalities of vision.	Mydriasis, see section 4.4.			
Ear and labyrinth disorders		Tinnitus.				
Cardiac disorders	Palpitations.	Tachycardia.	Bradycardia.		Supraventricular and ventricular arrhythmia.	QT-prolongation [1], ventricular arrhythmia including torsade de pointes [1].
Vascular disorders		Postural hypotension, hypotension, hypertension.		Haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, rectal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous membranes).		

	Very common	Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorders		Rhinitis, sinusitis, yawning.	Coughing.			Epistaxis.
Gastrointestinal disorders	Nausea, dry mouth, constipation, diarrhoea.	Dyspepsia, vomiting, abdominal pain, flatulence, increased salivation.				
Hepatobiliary disorders			Increased liver enzyme values.	Hepatitis.		Liver function test abnormal.
Skin and subcutaneous tissue disorders	Increased sweating.	Rash, Pruritus.	Photosensitivity reaction, urticaria, alopecia, purpura.		Angioedema.	Ecchymosis.
Musculoskeletal and connective tissue disorders		Myalgia, Arthralgia.				
Renal and urinary disorders		Micturition disorder, Polyuria.	Urinary retention.			
Reproductive system and breast disorders		Ejaculation failure, ejaculation disorder, female: menorrhagia, dysmenorrhoea, impotence.			Galactorrhoea.	Female: metrorrhagia, male: priapism, postpartum haemorrhage**.
General disorders and administration site conditions	Asthenia.	Fatigue.	Malaise, Oedema.	Pyrexia.		

[1] Cases of QT-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, 4.4, 4.5, 4.9 and 5.1).

* Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).

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

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

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to withdrawal 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 re-actions. 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 citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Symptoms
The following symptoms have been seen in reported overdose of 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, and atrial and ventricular arrhythmia.

Treatment
There is no known specific antidote to citalopram. Treatment should be symptomatic and supportive. Activated charcoal, osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered. If consciousness is impaired the patient should be intubated. Vital signs should be monitored.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, selective serotonin reuptake inhibitors
ATC code: N06A B04

Mechanism of action and pharmacodynamic effects
Tolerance to the inhibitory effect of citalopram on 5-HT uptake does not occur during long-term treatment.
The antidepressant effect is probably connected with the specific inhibition of serotonin uptake in the brain neurons.
Citalopram has almost no effect on the neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid. Citalopram shows no affinity, or only very little, for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.
Citalopram is a bi-cyclic isobenzofuran-derivative that is chemically not related to tricyclic and tetracyclic antidepressants or other available antidepressants. The main metabolites of citalopram are also selective serotonin uptake inhibitors, though to a lesser degree. The metabolites are not reported to contribute to the overall antidepressant effect.

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

General characteristics of the active substance

Absorption

Citalopram is rapidly absorbed following oral administration: the maximum plasma concentration is reached on average after 4 (1-7) hours. Absorption is independent of food intake. Oral bioavailability is approximately 80 %.

Distribution

The apparent distribution volume is 12-17 l/kg. The plasma-protein binding of citalopram and its metabolites is below 80 %.

Biotransformation

Citalopram is metabolised into desmethylcitalopram, didemethylcitalopram, citalopram-N-oxide and the deaminated propionic acid-derivative. The propionic acid-derivative is pharmacologically inactive. Desmethylcitalopram, didemethylcitalopram and citalopram-N-oxide are selective serotonin uptake inhibitors, although weaker than the parent compound.

In vivo research has demonstrated that the plasma levels of citalopram and its metabolites depend on the sparteine/debrisoquine phenotype and the mephenytoin phenotype. However, it is not necessary to dose individually according to these phenotypes.

Elimination

The plasma half-life is approximately 1½ days. After systemic administration, the plasma clearance is approximately 0.3-0.4 l/min and after oral administration the plasma clearance is approximately 0.4 l/min.

Citalopram is mainly eliminated via the liver (85 %), but also partly (15 %) via the kidneys. Of the quantity of citalopram administered, 12-23 % is eliminated unaltered via the urine. Hepatic clearance is approximately 0.3 l/min and renal clearance is 0.05-0.08 l/min.

Steady-state concentrations are reached after 1-2 weeks. A linear relationship has been demonstrated between the steady-state plasma level and the dose administered. At a dose of 40 mg per day, an average plasma concentration of approximately 300 nmol/l is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Characteristics relating to patients

Elderly (≥ 65 years)

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

Hepatic impairment

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.

Renal impairment

In patients with a mildly to moderately reduced renal function a longer half-life and a small increase in the exposure of citalopram has been observed. Citalopram is eliminated more slowly, without an important effect on the pharmacokinetics of citalopram.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Phospholipidosis has been observed in several organs following multiple administrations in

rats. The effect was reversible at discontinuation. Accumulation of phospholipids has been observed in long term animal studies with many cation-amphophilic drugs. The clinical relevance of these results is not clear.

Reproduction toxicity studies in rats have demonstrated skeletal anomalies in the offspring, but no increased frequency of malformations. The effects may be related to the pharmacological activity or may be a consequence of maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation period. The potential risk for humans is unknown.

Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Mannitol
Microcrystalline cellulose
Colloidal silica, anhydrous
Magnesium stearate

Coating:
Hypromellose
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

PVC/PVDC/Al blisters: 5 years

HDPE tablet container: 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Citalopram STADA 10 20 40 mg tablets, packed in PVC/PVDC/Al blisters are available in pack sizes of 10, 14, 20, 28, 30, 50, 56, 98 and 100 tablets per box, 100x1 unit dose blister

HDPE tablet container with a LDPE tamper evident cap containing 250, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2 – 18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBER

RVG 27633
RVG 27634
RVG 27635

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING / HERNIEUWING VAN DE VERGUNNING:

Citalopram STADA 10/20/40 mg filmomhulde tabletten: 12.03.2002/29.09.2011

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.4, 4.6 en 4.8: 19 februari 2021