Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citalopram Bluefish 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.49 mg citalopram hydrobromide, equivalent to 10 mg citalopram.

Excipients with known effect: Lactose monohydrate
Each tablet Citalopram Bluefish 10 mg contains 12.665 mg lactose (anhydrous).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Citalopram Bluefish 10 mg film-coated tablets are round, white tablets with a diameter of 6 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

4.2 Posology and method of administration

Posology

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.

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

Depression
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.

Elderly patients (>65 years):

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 10-20 mg daily. The recommended maximum dose for the elderly 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 since there are no clinical data in this population (creatinine clearance less than 30mL/min, see section 5.2).

Reduced hepatic function:
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 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function (see 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, (see section 5.2).

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 or 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 discontinuation 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).
- 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).
- Concomitant treatment with pimozide (see also section 4.5)

4.4 Special warnings and precautions for use

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

Paediatric population
Citalopram Bluefish 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 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 (see section 4.2).
Hyponatraemia
Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported rarely, predominantly in the elderly (female patients seem to be at particularly high risk), and generally reverses on discontinuation of therapy.

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 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 citalopram 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.

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

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.

ECT (electroconvulsive therapy)
There is little clinical information on the concurrent use of citalopram and electroconvulsive therapy (ECT), and caution is therefore advised.

Mania
Citalopram should be used with caution for patients with a history of mania/hypomanic- -depressive illness as a change towards the manic phase may occur. Use of citalopram should be discontinued in any patient who enters a manic phase.

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).

Serotonin Syndrome
In rare cases, serotonin syndrome, a potentially life-threatening condition, has been reported in patients using SSRIs. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. 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.

Buprenorphine
Concomitant administration of citalopram and buprenorphine may result in serotonin 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.

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

Renal impairment
Citalopram use in patients with severe impairment of renal function (creatinine clearance less than 20 ml/min) is not advised, as no information is available on use in these patients.(see 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.

St John's Wort (Hypericum perforatum)
Undesirable effects may occur more in concurrent use of citalopram and herbal medicines containing St John's wort (Hypericum perforatum). Citalopram and St John's wort products should therefore not be taken concurrently (see 4.5).

Insomnia and agitation
Insomnia and agitation may occur at the start of treatment. Dose titration may be useful.

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 hypokalemia, 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.
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.

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.

Withdrawal symptoms seen on discontinuation
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a recurrence prevention clinical trial with citalopram, adverse events after discontinuation of active treatment were seen in 40% of patients versus 20% in patients continuing 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

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).

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The tablets contain sodium. Citalopram Bluefish contains less than 1 mmol sodium (23 mg) per 10 mg, 20 mg and 40 mg tablets, that is to say essentially 'sodium-free'.

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: agitation, tremor, myoclonus, and hyperthermia.

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. fentiazine 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.

Pimozide
Co administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and Cmax of pimozide, although not consistently throughout the study. The co-administration of pimozide and 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 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
No pharmacodynamic interactions have been found in clinical studies in which 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 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.

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).

Citalopram 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).

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, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsychotics, phenothiazines, tricyclic depressants) 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 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 inducing hypokalaemia/hypomagnesaemia
Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias (see section 4.4).

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]), mefloquin, 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.

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, a known enzyme-inhibitor, caused a slight rise in the average steady-state citalopram levels. Caution is therefore recommended when administering citalopram in combination 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. Dose adjustment may be warranted.

Metoprolol
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 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
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 epoxid) and triazolam).

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit 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

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.

Pregnancy
Published data on pregnant women (more than 2500 exposed outcomes) indicate no malformative feto/ neonatal toxicity. However, citalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

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 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 withdrawal 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, particular 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).

Breastfeeding
Citalopram is excreted in 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.

4.7 Effects on ability to drive and use machines

Citalopram has a minor or moderate influence on the ability to drive and use machines.
Psychoactive medicinal products may reduce ability to assess ability to react to unexpected events. Patients should therefore be warned and informed that ability to drive and operate machines may be affected.

4.8 Undesirable effects

Adverse reactions 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 (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

MedDRA SOC	**Frequency**	**Preferred term**
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Not Known	Hypersensitivity , anaphylactic reaction
Endocrine disorders	Not Known	Inappropriate ADH secretion Hyperprolactinaemia
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased
	Uncommon	Increased appetite, weight increased
	Rare	Hyponatremia
	Not Known	Hypokalaemia
Psychiatric disorders	Common	Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female), abnormal dreams
	Uncommon	Aggression, depersonalization, hallucination, mania
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Very common	Somnolence, insomnia, headache
	Common	Tremor, paraesthesia, dizziness, disturbance in attention
	Uncommon	Syncope
	Rare	Convulsion grand mal, dyskinesia, taste disturbance
	Not Known	Convulsions , serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	Uncommon	Mydriasis
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not Known	QT-prolongation[1] , ventricular arrhythmia including torsade de pointes
Vascular disorders	Rare	Haemorrhage
	Not Known	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Common	Yawning
	Not Known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, Nausea
	Common	Diarrhoea vomiting, Constipation
	Not Known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis

	Not Known	Liver function test abnormal
Skin and subcutaneous tissue disorders	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura, photosensitivity reaction
	Not Known	Ecchymosis, angioedemas
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Impotence, ejaculation disorder, ejaculation failure
	Uncommon	Female: Menorrhagia
	Not Known	Female: Metrorrhagia, postpartum haemorrhage* Male: Priapism, galactorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema
	Rare	Pyrexia

Number of patients: Citalopram / placebo = 1346 / 545

[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 hypokalemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

[2] 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).

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 and TCAs. The mechanism leading to this risk is unknown.

Withdrawal symptoms seen on discontinuation

Discontinuation of 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 have been reported. 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 section 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 online reporting option (preferred method) accessible from the HPRA homepage (www. hpra.ie). A downloadable report form is also accessible from the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.
HPRA Pharmacovigilance
Website: www.hpra.ie

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 of overdose:

The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT interval 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 arrythmia.

Treatment of overdose:

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. ECG and 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

Pharmacotherapeuticgroup: Antidepressants, Selective serotonin reuptake inhibitors
ATC code: N06A B04

Mechanism of action and pharmacodynamic effects
Tolerance with respect to the inhibiting action on uptake of 5-HT does not occur in the long-term use of citalopram.
The antidepressant action is assumed to be associated with the specific inhibition of serotonin uptake in the neurons of the brain.
Citalopram has almost no effect on neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid. Citalopram shows no or only little affinity for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.

Citalopram is a bicyclic isobenzofuran derivative and is chemically not related to tricyclic, tetracyclic and other available antidepressants.

The principal metabolites of citalopram are, like citalopram, selective serotonin reuptake inhibitors, although to a lesser extent. As far as is known, the metabolites do not make any contribution to the therapeutic 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 ingredient:

Absorption:
Citalopram is rapidly absorbed after oral administration: the maximum plasma concentration is reached on average after around 4 (1-7) hours. Absorption is independent of any food intake. The biological availability is approximately 80 %.

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

Biotransformation:
Citalopram is metabolised into demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and the deaminated propionic acid-derivative. The propionic acid-derivative is pharmacologically inactive. Demethylcitalopram, didemethylcitalopram and citalopram-N-oxide are selective serotonin uptake inhibitors, although weaker than the parent compound.
The main metabolising enzyme is CYP2C19. Some contribution from CYP3A4 and CYP2D6 is possible.
Elimination:
Plasma half-life is approximately one and a half days. Plasma clearance following systemic administration is approximately 0.3-0.4 l/min and plasma clearance following oral administration is approximately 0.4 l/min.
Citalopram is principally excreted via the liver (85%) but partially (15%) also via the kidneys. 12-23% of the administered quantity of citalopram is excreted unchanged in 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 one to two weeks. A linear relation has been found between the steady-state plasma level and the administered dose. At a dosage of 40 mg daily a mean plasma concentration of approximately 300 nmol/l is reached. No clear relation has been found between the citalopram plasma level on the one hand and the therapeutic effect or possible adverse reactions on the other.

Characteristics relating to patients

Elderly patients (≥ 65 years)
Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

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.

There is no information on the pharmacokinetics in patients with severe renal impairment.

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 administration 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

Tablet core:
Copovidone
croscarmellose sodium (E468)
glycerol (E471)
lactose monohydrate
magnesium stearate (E470b)
maize starch
microcrystalline cellulose (E460)

Film coating:
Hypromellose (E464)
microcrystalline cellulose (E460)
macrogol stearate (E431)
titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 mg & 20 mg
Citalopram Bluefish 10 mg and 20 mg film-coated tablets packed in PVC/PVDC/Al blister are available in pack sizes of 14, 20, 28, 30, 50, or 100 tablets per carton.

Citalopram Bluefish 40 mg, film-coated tablets packed in PVC/PVDC/Al blister are available in pack sizes of 20, 28, 30, 50, or 100 tablets per carton.

Not all pack sizes/strengths may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1436/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th April 2010
Date of last renewal: 8th November 2014

10 DATE OF REVISION OF THE TEXT

March 2024