SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Citalopram Bluefish 10 mg film-coated tablets
Citalopram Bluefish 20 mg film-coated tablets
Citalopram Bluefish 40 mg film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Citalopram Bluefish 10 mg film-coated tablets:
Each tablet contains 12.49 mg citalopram hydrobromide, equivalent to 10 mg citalopram.

Citalopram Bluefish 20 mg film-coated tablets:
Each tablet contains 24.98 mg citalopram hydrobromide, equivalent to 20 mg citalopram.

Citalopram Bluefish 40 mg film-coated tablets:
Each tablet contains 49.96 mg citalopram hydrobromide, equivalent to 40 mg citalopram.

Excipients: Lactose monohydrate
Each tablet Citalopram Bluefish 10 mg contains 12.665 mg lactose (anhydrous).
Each tablet Citalopram Bluefish 20 mg contains 25.330 mg lactose (anhydrous).
Each tablet Citalopram Bluefish 40 mg contains 50.659 mg lactose (anhydrous).

For a 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.

Citalopram Bluefish 20 mg film-coated tablets are oval, white tablets scored and with a diameter of 8 mm.

Citalopram Bluefish 40 mg film-coated tablets are oval, white tablets scored and with a diameter of 11 mm.

The 20mg and 40mg tablet can be divided into equal halves.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Treatment of major depressive episodes.

4.2 Posology and 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.
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.

Use in children and adolescents under 18 years of age
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.

### 4.3 Contraindications

- Hypersensitivity to citalopram or any of the excipients.
• 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

Use in children and adolescents under 18 years of age:
Citalopram Bluefish should not be used in the treatment of children and adolescents under the age of 18 years (see 4.4). Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (principally 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.

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/hypomania. 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). 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).

Serotonine Syndrome
There have been rare reports of the occurrence of serotonin syndrome during use of SSRIs. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia, may indicate the development of this syndrome. 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.

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 30 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).

Dose titration
Drowsiness 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.

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 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 have been reported. 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).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interactions with other medicinal products and other forms of interaction
Pharmacodynamic interactions:

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).

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.

5-HT-agonists
The serotonergic action of sumatriptan may be reinforced by SSRIs. Until further information is available, concurrent use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, tramadol, oxitriptan and tryptophan is not advised (see section 4.4).

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).

Contraindicated combinations

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, antipsycotics (e.g. fentiazine deriviatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacín, moxifloxacín, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

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).

**Neuroleptics**
Experience with citalopram use has not provided evidence of any clinically relevant interactions with neuroleptics. The possibility of a pharmacodynamic interaction, as with other SSRIs, cannot, however, be ruled out.

**St. John’s Wort (Hypericum perforatum)**
Adverse reactions may occur more in concurrent use of citalopram and herbal medicinal products containing St John’s wort (Hypericum perforatum) (see section ).

**Alcohol**
Clinical studies have not shown any adverse pharmacodynamic or pharmacokinetic interactions between citalopram and alcohol. However, the combination of citalopram and alcohol is not advised.

**Pharmacokinetic interactions:**

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**Cytochrome P450 (CYP) isoenzymes**

- Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortryptyline 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.

- The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

**Influence of other medicinal products on the pharmacokinetics of citalopram**

- 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, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

**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.

**Lithium, tryptophan**
Citalopram does not show any pharmacokinetic interaction with lithium. There are, however, reports of increased serotonergic effects when SSRIs are administered in combination with lithium or tryptophan. Caution should therefore be exercised in the concurrent use of citalopram and these agents.
The lithium level should be monitored as usual.

*Levopromazine, digoxine, carbamazepine*
No pharmacokinetic interaction was found between citalopram and levomepromazine, digoxin or carbamazepine and the metabolite carbamazepine epoxide.

**Food**
The absorption and other pharmacokinetic properties of citalopram are not affected by food.

### 4.6 Pregnancy and lactation

**Pregnancy**
There are limited data from the use of citalopram in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Citalopram should not be used during pregnancy unless clearly necessary.

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. 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.

**Lactation**
Citalopram is excreted in breast milk in small quantities. The advantage of breastfeeding should outweigh the potential undesirable effects for the child.

### 4.7 Effects on ability to drive and use machines
Citalopram has a minor or moderate effect 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

Undesirable reactions to citalopram are generally mild and transient in nature. They mostly occur during the first weeks of treatment and usually decrease as the depressive condition improves.

Treatment emergent adverse events reported in clinical trials:

The following undesirable effects have been reported at the approximate frequencies shown:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>(≥ 1/10)</td>
</tr>
<tr>
<td>Common</td>
<td>(≥ 1/100, &lt; 1/10)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>(≥ 1/1000, ≤ 1/100)</td>
</tr>
<tr>
<td>Rare</td>
<td>(≥ 1/10000, ≤ 1/1000)</td>
</tr>
<tr>
<td>Very rare</td>
<td>(≤ 1/10000)</td>
</tr>
<tr>
<td>Not known</td>
<td>cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Rare: haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous membranes).

Metabolism and nutrition disorders

Common: weight decrease, weight increase.

Psychiatric disorders

Very common: somnolence, insomnia, agitation, nervousness.

Common: sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, confusion.

Uncommon: euphoria, increased libido.

Rare: psychomotor restlessness/akathisia (see section 4.4).

Very rare: hallucinations, mania, depersonalisation, panic attack (these symptoms may be due to the underlying disease).

Not known: suicidal thoughts/behaviour (cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation [see section 4.4]).

Nervous system disorders

Very common: headache, tremor, dizziness.

Common: migraine, paraesthesia.

Uncommon: extrapyramidal disorder, convulsions.
Eye disorders
Very common: abnormal accommodation.
Common: abnormalities of vision.

Ear and labyrinth disorders
Uncommon: tinnitus.

Cardiac disorders
Very common: palpitations.
Common: tachycardia.
Uncommon: bradycardia.
Very rare: supraventricular and ventricular arrhythmia.
Not known: ventricular arrhythmia including torsade de pointes

Vascular disorders
Common: postural hypotension, hypotension, hypertension.

Respiratory, thoracic and mediastinal disorders
Common: rhinitis, sinusitis.
Uncommon: coughing.

Gastrointestinal disorders
Very common: nausea, dry mouth, constipation, diarrhoea.
Common: dyspepsia, vomiting, abdominal pain, flatulence, increased salivation.

Hepatobiliary disorders
Uncommon: increased liver enzyme values.

Skin and subcutaneous tissue disorders
Very common: increased sweating.
Common: rash, pruritus.
Uncommon: photosensitivity.
Very rare: angiodema.

Musculoskeletal and connective tissue disorders
Uncommon: myalgia.
Very rare: arthralgia.

Renal and urinary disorders
Common: micturition disorder, polyuria.
Rare: hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), predominantly in the elderly (see section 4.4).

Reproductive system and breast disorders
Common: ejaculation failure, female anorgasmia, dysmenorrhoea, impotence.
Very rare: galactorrhoea.

General disorders and administration site conditions
Very common: asthenia.
Common: fatigue, yawning, taste abnormalities.
Uncommon: allergic reactions, syncope, malaise.
Rare: serotonin syndrome has been reported in patients using SSRIs.
Very rare: anaphylactic reactions.

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).

Withdrawal symptoms seen on discontinuation
Discontinuation of citalopram (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 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).

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

4.9 Overdose

Symptoms of overdose:
Somnolence, coma stupor, seizures, ECG changes (e.g. prolonged QT interval), atrial and ventricular arrhythmia, nausea, vomiting, transpiration, cyanosis, hyperventilation. Features of serotonin syndrome may occur, particularly when other substances are co-ingested.

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
Pharmacotherapeutic group: 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.

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

Citalopram Bluefish 10 mg, 20 mg and 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 instructions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
Torgatan 11
SE-111 23 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2009-09-11

10. DATE OF REVISION OF THE TEXT

2012-02-13