



## **Public Assessment Report**

**Name of the Product:**

**Escitalopram Teva**

**5 mg, 10 mg, 15 mg and 20 mg film-coated tablets**

**(escitalopram)**

**Procedure number:**

**HU/H/0179/001/DC**

**HU/H/0179/002/DC**

**HU/H/0179/003/DC**

**HU/H/0179/004/DC**

**Marketing authorisation holder:**

**Teva Magyarország Zrt. (Teva Hungary plc)**

**Date: 23 August 2013**

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE  
ON THE PUBLIC ASSESSMENT REPORT

## LAY SUMMARY

After careful consideration of their quality and therapeutic benefit/risk ratio, the National Institute of Pharmacy Directorate of the *National Institute for Quality- and Organizational Development in Healthcare and Medicines* issued marketing authorisation for the Escitalopram (in Hungary: Escitalopram Teva) 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. The holder of the marketing authorisation is Teva Magyarország Zrt. in Hungary.

The Escitalopram film-coated tablets contain the active substance escitalopram (as oxalate). Their other ingredients are:

- core: microcrystalline cellulose, colloidal silica anhydrous, croscarmellose sodium, stearic acid and magnesium stearate;
- coating: hypromellose (E464), macrogol 400, and titanium dioxide (E171).

The 5 mg tablets are white, marked “93” on one side and “7414” on the other.

The 10 mg tablets are white, scored on one side and marked “9” on one side and “3” on the other. The other side of the tablet is marked “7462”. The tablets can be divided into equal halves.

The 15 mg tablets are white, scored on one side and marked “S” on one side and “C” on the other. The other side of the tablet is marked “15”. In case the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The 20 mg tablets are white, scored on one side and marked “9” on one side and “3” on the other. The other side of the tablet is marked “7463”. The tablets can be divided into equal halves.

The film-coated tablets are marketed in blister packs or in perforated unit dose blister.

Escitalopram belongs to a group of antidepressants called selective serotonin reuptake inhibitors (SSRIs). These medicines act on the serotonin-system in the brain by increasing the serotonin level. Disturbances in the serotonin-system are considered an important factor in the development of depression and related diseases.

The Escitalopram film-coated tablets and are used to treat depression (major depressive episodes) and anxiety disorders (such as panic disorder with or without agoraphobia, social anxiety disorder, generalised anxiety disorder and obsessive-compulsive disorder).

### **What you need to know before taking Escitalopram film-coated tablets**

*Do not take this product if you*

- are allergic (hypersensitive) to escitalopram or any of the other ingredients of the film-coated tablets;
- take other medicines that belongs to a group called MAO inhibitors, including selegiline (used in the treatment of Parkinson’s disease), moclobemide (used in the treatment of depression) and linezolid (an antibiotic);

- are born with or have had an episode of abnormal heart rhythm (seen at ECG; an examination to evaluate how the heart is functioning);
- take medicines for heart rhythm problems or that may affect the heart's rhythm.

### *Warnings and precautions*

Inform your doctor before taking Escitalopram film-coated tablets if you

- have epilepsy. Treatment with escitalopram should be stopped if seizures occur for the first time or if there is an increase in the seizure frequency;
- suffer from impaired liver or kidney function. Your doctor may need to adjust your dosage;
- have diabetes. Treatment with escitalopram may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted;
- have a decreased level of sodium in the blood;
- have a tendency to easily develop bleedings or bruises;
- are receiving electroconvulsive treatment;
- have coronary heart disease;
- suffer or have suffered from heart problems or have recently had a heart attack;
- have a low resting heart-rate and/or you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets);
- experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up, which may indicate abnormal functioning of the heart rate.

### *Note*

Some patients with manic-depressive illness may enter into a manic phase. This is characterized by unusual and rapidly changing ideas, inappropriate happiness and excessive physical activity. If you experience this, contact your doctor.

Symptoms such as restlessness or difficulty to sit or stand still can also occur during the first weeks of the treatment. Tell your doctor immediately if you experience these symptoms.

### *Thoughts of suicide and worsening of your depression or anxiety disorder*

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourselves. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you

- have previously had thoughts about killing or harming yourself;
- are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think

your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

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

Escitalopram film-coated tablets should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side effects such as suicide attempts, suicidal thoughts and hostility (predominately aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe escitalopram for patients under 18 because he/she decides that this is in their best interest. If your doctor has prescribed escitalopram for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any symptoms listed above develop or worsen when patients under 18 are taking escitalopram. Also, the long term safety effects concerning growth, maturation and cognitive and behavioural development of escitalopram in this age group have not yet been demonstrated.

#### *Other medicines and Escitalopram film-coated tablets*

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicine, particularly

- "non-selective monoamine oxidase inhibitors (MAOIs)", containing phenelzine, iproniazid, isocarboxazid, nialamide, and tranylcypromine as active ingredients. If you have taken any of these medicines you will need to wait 14 days before you start taking escitalopram. After stopping escitalopram tablets you must allow 7 days before taking any of these medicines;
- "reversible, selective MAO-A inhibitors", containing moclobemide (used to treat depression).
- "Irreversible MAO-B inhibitors", containing selegiline (used to treat Parkinson's disease). These increase the risk of side effects;
- the antibiotic linezolid;
- lithium (used in the treatment of manic-depressive disorder) and tryptophan;
- imipramine and desipramine (both used to treat depression);
- sumatriptan and similar medicines (used to treat migraine) and tramadol (used against severe pain). These increase the risk of side effects;
- cimetidine and omeprazole (used to treat stomach ulcers), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). These may cause increased blood levels of escitalopram;
- St. John's Wort (*Hypericum perforatum*) – a herbal remedy used for depression;
- Acetylsalicylic acid and non-steroidal anti-inflammatory drugs (medicines used for pain relief or to thin the blood, so called anti-coagulant). These may increase bleeding-tendency;
- warfarin, dipyridamole, and phenprocoumon (medicines used to thin the blood, so called anti-coagulant). Your doctor will probably check the coagulation time of your blood when starting and discontinuing Escitalopram film-coated tablets in order to verify that your dose of anti-coagulant is still adequate;
- mefloquin (used to treat malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain) due to a possible risk of a lowered threshold for seizures;
- neuroleptics (medicines to treat schizophrenia, psychosis) due to a possible risk of a lowered threshold for seizures, and antidepressants;

- flecainide, propafenone, and metoprolol (used in cardio-vascular diseases) clomipramine, and nortriptyline (antidepressants) and risperidone, thioridazine, and haloperidol (antipsychotics). The dosage of escitalopram may need to be adjusted.

Do not take Escitalopram film-coated tablets if you take medicines for heart rhythm problems or medicines that may affect the heart's rhythm, 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-malaria treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine).

#### *Taking Escitalopram film-coated tablets with food and drink*

Escitalopram film-coated tablets can be taken with or without food.

As with many medicines, combining Escitalopram film-coated tablets with alcohol is not advisable, although escitalopram is not expected to interact with alcohol.

#### *Fertility, pregnancy and breast-feeding*

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine for taking Escitalopram film-coated tablets if you are pregnant or breast-feeding is not advisable unless you and your doctor have discussed the risks and benefits involved.

Citalopram, a medicine like escitalopram, has been shown to reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.

If you take Escitalopram film-coated tablets during the last 3 months of your pregnancy you should be aware that the following effects may be seen in your newborn baby: trouble with breathing, bluish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. If your newborn baby has any of these symptoms, please contact your doctor immediately.

Make sure your midwife and/or doctor know you are on Escitalopram film-coated tablets. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Escitalopram film-coated tablets may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

If used during pregnancy Escitalopram film-coated tablets should never be stopped abruptly.

### *Driving and using machines*

You are advised not to drive a car or operate machinery until you know how Escitalopram film-coated tablets affect you.

### **How to take Escitalopram film-coated tablets**

#### Adults

- depression: the normally recommended dose is 10 mg taken as one daily dose. The dose may be increased by your doctor to a maximum of 20 mg per day;
- panic disorder: the starting dose is 5 mg as one daily dose for the first week before increasing the dose to 10 mg per day. The dose may be further increased by your doctor to a maximum of 20 mg per day;
- social anxiety disorder: the normally recommended dose is 10 mg taken as one daily dose. Your doctor can either decrease your dose to 5 mg per day or increase the dose to a maximum of 20 mg per day, depending on how you respond to the medicine;
- generalised anxiety disorder: the normally recommended dose is 10 mg taken as one daily dose. The dose may be increased by your doctor to a maximum of 20 mg per day;
- obsessive-compulsive disorder: the normally recommended dose is 10 mg taken as one daily dose. The dose may be increased by your doctor to a maximum of 20 mg per day.

Elderly patients (above 65 years of age): the recommended starting dose of escitalopram is 5 mg taken as one daily dose. The dose may be increased by your doctor to 10 mg per day.

Children and adolescents (below 18 years of age): Escitalopram film-coated tablets should not normally be given to children and adolescents.

You can take Escitalopram film-coated tablets with or without food. Swallow the tablet with some water. Do not chew them, as the taste is bitter.

### *Duration of treatment*

It may take a couple of weeks before you start to feel better. Continue to take Escitalopram film-coated tablets even if it takes some time before you feel any improvement in your condition.

Do not change the dose of your medicine without talking to your doctor first.

Continue to take Escitalopram film-coated tablets for as long as your doctor recommends. If you stop your treatment too soon, your symptoms may return. It is recommended that treatment should be continued for at least 6 months after you feel well again.

### *What happens if you take more Escitalopram film-coated tablets than prescribed*

If you take more than the prescribed dose of Escitalopram film-coated tablets, contact your doctor or nearest hospital emergency department immediately. Do this even if there are no signs of discomfort. Some of the signs of an overdose could be dizziness, tremor, agitation,

convulsion, coma, nausea, vomiting, change in heart rhythm, decreased blood pressure and change in body fluid/salt balance. Take the Escitalopram film-coated tablets box/container with you when you go to the doctor or hospital.

*What happens if you forget to take Escitalopram film-coated tablets*

Do not take a double dose to make up for forgotten doses. If you do forget to take a dose, and you remember before you go to bed, take it straight away. Carry on as usual the next day. If you only remember during the night, or the next day, leave out the missed dose and carry on as usual.

*If you stop taking Escitalopram film-coated tablets*

Do not stop taking Escitalopram film-coated tablets until your doctor tells you to do so. When you have completed your course of treatment, it is generally advised that the dose is gradually reduced over a number of weeks.

When you stop taking Escitalopram film-coated tablets, especially if it is abruptly, you may feel discontinuation symptoms. These are common when treatment with escitalopram is stopped. The risk is higher, when Escitalopram film-coated tablets have been used for a long time or in high doses or when the dose is reduced too quickly. Most people find that the symptoms are mild and go away on their own within two weeks. However, in some patients they may be severe in intensity or they may be prolonged (2-3 months or more). If you get severe discontinuation symptoms when you stop taking Escitalopram film-coated tablets, please contact your doctor. He or she may ask you to start taking your tablets again and come off them more slowly.

Discontinuation symptoms include: feeling dizzy (unsteady or off-balance), feelings like pins and needles, burning sensations and (less commonly) electric shock sensations, including in the head, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling anxious, headaches, feeling sick (nausea), sweating (including night sweats), feeling restless or agitated, tremor (shakiness), feeling confused or disorientated, feeling emotional or irritable, diarrhoea (loose stools), visual disturbances, fluttering or pounding heartbeat (palpitations).

### **Possible side effects**

Like all medicines, Escitalopram film-coated tablets can cause side effects, although not everybody experiences them.

The side effects usually disappear after a few weeks of treatment. Please be aware that many of the effects may also be symptoms of your illness and therefore will improve when you start to get better.

If you experience the following side effects you should contact your doctor or go to the hospital straight away:

- uncommon (that may affect up to 1 in 100 people): unusual bleeds, including gastrointestinal bleeding.
- rare (that may affect up to 1 in 1,000 people):

- swelling of skin, tongue, lips, or face, or have difficulties breathing or swallowing (allergic reaction),
- high fever, agitation, confusion, trembling and abrupt contractions of muscles these may be signs of a rare condition called serotonin syndrome.

Some patients have reported also the following adverse effects (their frequency can not be estimated from the available data):

- fast, irregular heart beat, fainting which could be symptoms of a life-threatening condition known as Torsades de Pointes,
- difficulties urinating,
- seizures (fits),
- yellowing of the skin and the white in the eyes are signs of liver function impairment/hepatitis.

In addition to above the following side effects have been reported:

- very common (that may affect more than 1 in 10 people): feeling sick (nausea);
- common (that may affect up to 1 in 10 people):
  - blocked or runny nose (sinusitis),
  - decreased or increased appetite;
  - anxiety, restlessness, abnormal dreams, difficulties falling asleep, feeling sleepy, dizziness, yawning, tremors, prickling of the skin,
  - diarrhoea, constipation, vomiting, dry mouth,
  - increased sweating,
  - pain in muscle and joints (arthralgia and myalgia),
  - sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties achieving orgasm),
  - fatigue, fever,
  - increased weight;
- uncommon (that may affect up to 1 in 100 people):
  - nettle rash (urticaria), rash, itching (pruritus),
  - grinding one's teeth, agitation, nervousness, panic attack, confusion state,
  - disturbed sleep, taste disturbance, fainting (syncope),
  - enlarged pupils (mydriasis), visual disturbance, ringing in the ears (tinnitus),
  - loss of hair,
  - vaginal bleeding,
  - decreased weight,
  - fast heart beat,
  - swelling of the arms or legs,
  - nosebleeds;
- rare (that may affect up to 1 in 1,000 people)
  - aggression, depersonalisation, hallucination,
  - slow heart beat.

Some patients have reported the following adverse effects (their frequency can not be estimated from the available data):

- thoughts of harming yourself or thoughts of killing yourself,

- decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused),
- dizziness when you stand up due to low blood pressure (orthostatic hypotension),
- abnormal liver function test (increased amounts of liver enzymes in the blood),
- movement disorders (involuntary movements of the muscles),
- painful erections (priapism),
- bleeding disorders including skin and mucous bleeding (ecchymosis) and low level of blood platelets (thrombocytopenia),
- sudden swelling of skin or mucosa (angioedemas),
- increase in the amount of urine excreted (inappropriate ADH secretion),
- flow of milk in women that are not nursing,
- mania,
- increased risk of bone fractures,
- alteration of the heart rhythm (called “prolongation of QT interval”, seen on ECG, electrical activity of the heart).

In addition, a number of side effects are known to occur with drugs that act in a similar way to escitalopram, such as

- motor restlessness (akathisia),
- anorexia.

### **How to store Escitalopram film-coated tablets**

Escitalopram film-coated tablets should be stored below 30 °C in the original package (carton) in order to protect from light and moisture. They should be kept out of the sight and reach of children.

## Scientific discussion

**This module reflects the scientific discussion for the approval of Escitalopram Teva 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised at 22 May 2012. For information on changes after this date please refer to the module 'Update'.**

## I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use* (implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products* as well as by the Decree 52/2005 (XI. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary), an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (reference member state, RMS: Hungary, concerned member states, CMS: AT, BG, CY, DK, EE, EL, FI, IE, LT, LV, MT, NO, PL, PT, RO, SI and SK) concerned escitalopram 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products, Cipramil and CipraleX tablets, have currently been licensed in many Member States (in Sweden since 2001) for the treatment of major depressive episode; treatment of panic disorder with or without agoraphobia; treatment of social anxiety disorder (social phobia); treatment of generalised anxiety disorder; and treatment of obsessive-compulsive disorder.

The active ingredient of CipraleX tablets is escitalopram (the S-(+)-isomer) while that of Cipramil tablets is the racemate (both the S-(+)- and R-(-)-isomers). Only the escitalopram is responsible for the desired antidepressant action.

Considering the adequateness of the reference medicinal products the RMS considered the following:

- according to Article 10(2b) of the Directive 2001/83/EC, “the different... isomers, mixtures of isomers... of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy”;
- the dosage regimen of citalopram containing products is twofold in relation to that of escitalopram products strengthening the view that only the S-(+)-isomer is responsible for the antidepressant action;
- at the time of the application, no convincing proof on difference of safety profiles of the above corresponding doses of citalopram and escitalopram was available.

To support the submission, the applicant Teva conducted a bioequivalence study in which its 10 mg escitalopram tablet was compared to 10 mg CipraleX (sourced from Denmark) and also 20 mg Cipramil tablets (sourced from England). Appropriate comparative dissolution studies for the 5 mg, 15 mg and 20 mg tablet strengths were also conducted demonstrating that all requirements of granting biowaiver were fulfilled. The applicant stated that the bioequivalence study was conducted according to Good Clinical Practice (GCP).

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Escitalopram (in Hungary: Escitalopram Teva) 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets.

The Escitalopram film-coated tablets are used to treat depression (major depressive episodes) and anxiety disorders (such as panic disorder with or without agoraphobia, social anxiety disorder, generalised anxiety disorder and obsessive-compulsive disorder).

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

## II. QUALITY ASPECTS

### II.1 Introduction

The Applicant stated that this product has been developed by Teva to be essentially similar to the original product CipraleX 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets of the innovator H. Lundbeck A/S. CipraleX film-coated tablets have been marketed in the European Economic Area since 2001, in Hungary since 2002.

The products are formulated as dose proportional film-coated tablets, containing escitalopram oxalate as drug substance. Citalopram is a well-known antidepressant drug available on the market; it is included in the pharmacotherapeutic group of antidepressants, selective serotonin re-uptake inhibitors. Escitalopram is the S-isomer of citalopram and it has been identified as the responsible one of the therapeutic effect of the racemate.

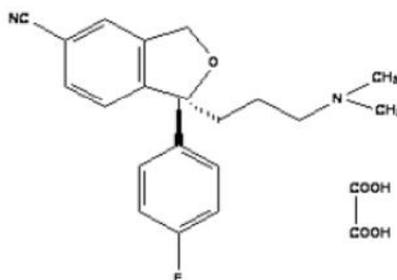
### II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN: escitalopram oxalate

Chemical name: S-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate

Structure:



Molecular formula:  $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$

Relative molecular mass: 414

The active substance is white to almost white fine crystalline powder. It shows polymorphism, freely soluble in methanol and in dimethyl sulphoxide. It has been demonstrated that the manufacturer consistently produces the correct enantiomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. The proposed manufacturing process has been adequately described; critical steps and accompanying in-process controls have been defined to ensure quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.

Evidence of the structure has been confirmed by elemental analysis, IR, NMR, MS, UV spectroscopy and by X-Ray Powder Diffraction data. Potential impurities originating from starting materials, intermediates, by-products and degradation products have been discussed in relation to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.

Escitalopram oxalate is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the active substance, which includes the following tests: description, solubility, identification of escitalopram by IR and UV, identification of oxalic acid by HPLC, specific optical rotation, water content, melting range, sulphated ash, heavy metals, enantiomeric purity, related substances (chromatographic purity), assay, residual solvents and particle size distribution.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Conference on Harmonisation (ICH) Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Ph. Eur. are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance in double polyethylene bag placed in a fibre drum. According to the presented stability data the proposed re-test period is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

### **II.3 Medicinal Product**

The aim of the pharmaceutical development was to produce immediate-release film-coated tablets containing escitalopram oxalate as drug substance in 5 mg, 10 mg, 15 mg and 20 mg doses bioequivalent to the reference medicinal product CipraleX film-coated tablets marketed by Lundbeck A/S.

A satisfactory package of data on development pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

The drug product is presented in four dosage strengths as white, film-coated standard convex tablets,

- the 5 mg tablet is engraved with “93” on one side and “7414” on the other side of the tablet;
- the 10 mg tablet is scored on one side and engraved with "9" on the left side of the score and "3" on the right side of the score. The other side is engraved with "7462";
- the 15 mg tablet is scored on one side and engraved with "S" on the left side of the score and "C" on the right side of the score. The other side is engraved with "15";
- the 20 mg tablet is scored on one side and engraved with "9" on the left side of the score and "3" on the right side of the score. The other side is engraved with "7463".

The scorelines are intended to facilitate breaking for ease of swallowing in case of the 15 mg tablets, and for dividing into equal doses in case of the 10 and 20 mg tablets.

Tablets are packed into transparent PVC/PVdC//Al blisters. The blisters are packed into cardboard cartons.

The excipients used in the finished product are colloidal anhydrous silica, magnesium stearate, stearic acid, croscarmellose sodium, microcrystalline cellulose and as a film-coating Opadry White. These excipients are commonly used in the pharmaceutical industry for solid oral dose presentations and they are standard pharmacopoeial materials except for the coating agent, but the components of the latter are also described in the Ph. Eur.

Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline.

Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Standard pharmacopoeial methods are used in respect of microbiological contamination and uniformity of dosage units of subdivided tablets where it is relevant.

Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

Certificates of analysis were also provided for the working standard used.

The container closure system of the product is as follows: transparent, colourless PVC/PVdC//Al blisters and box. The same blisters as those proposed for routine storage were used for the stability studies. The selected primary packaging material complies with the relevant Ph. Eur. Monograph and foodstuff legislation.

Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years if stored below 25 °C in the original packaging in order to protect from moisture is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

#### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical and pharmaceutical aspects the product is approvable.

### III. NON-CLINICAL ASPECTS

#### III.1 Introduction

This application relates the generic version of escitalopram tablets.

Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram are well known. As it is widely used, well-known active substance, the applicant did not provide additional studies and further studies are not required. Overview based on literature review was, thus, appropriate.

#### III.2 Pharmacology

Escitalopram is the S-enantiomer of racemic citalopram and has been demonstrated to be the only pharmacologically active component in the racemic mixture.

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity.

Escitalopram has no or low affinity for a number of receptors including 5-HT<sub>1A</sub>, 5-HT<sub>2</sub>, DA D<sub>1</sub> and D<sub>2</sub> receptors,  $\alpha_1$ -,  $\alpha_2$ -,  $\beta$ -adrenoceptors, histamine H<sub>1</sub>, muscarine cholinergic, benzodiazepine, and opioid receptors.

The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

#### III.3 Pharmacokinetics

The absorption of escitalopram is almost complete and independent of food intake. As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

The plasma protein binding is below 80% for escitalopram and its main metabolites.

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides.

Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine. The pharmacokinetics is linear.

### III.4 Toxicology

No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted in rats with escitalopram and citalopram showed a similar profile. Therefore, all citalopram information can be extrapolated to escitalopram.

In comparative toxicological studies in rats, escitalopram and citalopram caused cardiac toxicity, including congestive heart failure, after treatment for some weeks, when using dosages that caused general toxicity. The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3- to 4-fold higher than the exposure achieved in clinical use. For citalopram, AUC values for the S-enantiomer were 6- to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and ischemia. However, the exact mechanism of cardiotoxicity in rats is not clear. Clinical experience with citalopram and the clinical trial experience with escitalopram do not indicate that these findings have a clinical correlate.

Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment cessation. Accumulation of phospholipids (phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this phenomenon has any significant relevance for man.

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. No animal data related to this aspect are available for escitalopram.

In the developmental toxicity study in the rat, embryotoxic effects (reduced foetal weight and reversible delay of ossification) were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. A pre- and postnatal study showed reduced survival during the lactation period at exposures in terms of AUC in excess of the exposure achieved during clinical use.

### III.5 Ecotoxicity/environmental risk assessment

Since the Escitalopram film-coated tablets are intended for generic substitution, this would not lead to an increased exposure to the environment. Therefore, no environmental risk assessment deemed necessary.

### **III.6 Discussion on the non-clinical aspects**

The application was based on Article 10(1) of Directive 2001/83/EC, generic application. No new non-clinical data has been submitted. Escitalopram is a well established compound with the pharmacodynamic, pharmacokinetic and toxicological properties being well known.

The use of the proposed generic product is not expected to be associated with any new toxicological hazards.

The non-clinical part of the application is acceptable.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

This application was submitted under Article 10(1) of the Directive 2001/83/EC (generic submission). Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram are well known.

The applicant adequately summarized the clinical experience with escitalopram.

Escitalopram is the S-enantiomer of racemic citalopram and has been demonstrated to be the only pharmacologically active component in the racemic mixture. Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site.

No new clinical studies apart from the bioequivalence study were submitted with this application. This is acceptable for one the one hand it was a generic application, on the other hand escitalopram is a well known active ingredient and no clinical issues are considered to arise as a result of its inclusion in the proposed product.

### IV.2 Pharmacokinetics

#### *IV.2.1 Literature data*

Absorption is almost complete and independent of food intake. Mean  $t_{max}$  is reached on average after 4 hours after multiple dosing. As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

The apparent volume of distribution ( $V_d, \beta/F$ ) after oral administration is about 12 to 26 l/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites.

Biotransformation: escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

The elimination half-life after multiple dosing is about 30 hours and the oral plasma clearance is about 0.6 l/min. The major metabolites have a significantly longer half-life.

Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

There is linear pharmacokinetics. Steady-state plasma levels are achieved in about 1 week.

Elderly patients (> 65 years): escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers.

Reduced hepatic function: in patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function.

Reduced renal function: with racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CL<sub>cr</sub> 10-53 ml/min).

Polymorphism: it has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers.

#### **IV.2.2 Bioequivalence study**

To support the application, the applicant submitted a bioequivalence study titled: “A Single-Dose, Comparative Bioavailability Study of Two Formulations of Escitalopram 10 mg Tablets and One Formulation of Citalopram 20 mg Tablets under Fasting Conditions”

This was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover study designed to evaluate the comparative bioavailability between Escitalopram oxalate 10 mg tablets (A) and CipraleX 10 mg escitalopram tablets (B) or Cipramil 20 mg citalopram tablets (C) administered to healthy male subjects under fasting conditions.

Subjects were randomly assigned to one of the six dosing sequences ABC, ACB, BAC, BCA, CAB, or CBA under fasting conditions.

The reason of this unusual three-arm design was that actually there were two reference products in this bioequivalence study. B is the escitalopram tablet of the originator and the second reference (C) was citalopram. However, regarding this application only comparison between A and B is relevant.

Blood sampling were taken at predose (t=0) and at appropriate postdose intervals.

Healthy male volunteers were enrolled in the study; their number was based on a statistical sample size determination.

The bioequivalence assessment was done using a parametric approximation for AUC and C<sub>max</sub> after log-transformation. The ratios of C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were reported.

ANOVA was performed in order to evaluate formulation, sequence and period effect. Software packages were applied for the analysis. The 90% confidence intervals for the

difference between the drug formulations were calculated for the parameters ( $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ ). The statistical significance was established at  $p \leq 0.05$ .

**Escitalopram pharmacokinetic parameters A vs. B**

Parameter	Geometric means Arithmetic means		A/B	
	Treatment A Escitalopram 10 mg	Treatment B CipraleX 10 mg	ratio of geometric means (%)	90% confi- dence inter- val (%)
<b>AUC<sub>0-t</sub></b> <b>(ng.h/ml)</b>	338.448 356.005	336.581 357.527	100.55	95.91 - 105.42
<b>AUC<sub>0-∞</sub></b> <b>(ng.h/ml)</b>	365.274 393.556	362.238 393.126	100.84	96.21 - 105.68
<b>C<sub>max</sub></b> <b>(ng/ml)</b>	9.857 9.939	9.664 9.883	101.99	97.43 - 106.77
<b>T<sub>max</sub><sup>a</sup> (h)</b>	4.67	4.36	–	–

<sup>a</sup>presented as arithmetic mean only.

The table confirms that the point estimates of the ‘test/reference’ mean ratios of the variables  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for Teva escitalopram vs. CipraleX are 100.55% and 100.84% respectively. The point estimate of the ‘test/reference’ mean ratio of the variable  $C_{max}$  for S-citalopram is 101.99%.

Based on the submitted bioequivalence study Escitalopram Oxalate 10 mg tablet Teva is considered bioequivalent with the originator CipraleX 10 mg tablet.

In the original statistical report several other comparisons were made. They are not relevant in this application and, consequently, they are not repeated here.

The applicant stated that the bioequivalence study had been conducted according to Good Clinical Practice (GCP).

Biowaiver: appropriate comparative dissolution studies for the 5 mg, 15 mg and 20 mg tablet strengths were also conducted demonstrating that all requirements of granting biowaiver are fulfilled.

### IV.3 Pharmacodynamics

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity.

Escitalopram has no or low affinity for a number of receptors including 5-HT<sub>1A</sub>, 5-HT<sub>2</sub>, DA D<sub>1</sub> and D<sub>2</sub> receptors,  $\alpha$ <sub>1</sub>-,  $\alpha$ <sub>2</sub>-,  $\beta$ -adrenoceptors, histamine H<sub>1</sub>, muscarine cholinergic, benzodiazepine, and opioid receptors.

The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

#### **IV.4 Clinical efficacy**

The efficacy of escitalopram has already been demonstrated during the clinical development of the reference product. No new data have been submitted that is acceptable for generic submissions.

#### **IV.5 Clinical safety**

The clinical safety of escitalopram has been well established. The bioequivalence study did not raise any new safety concerns.

#### **IV.6 Discussion on the clinical aspects**

The application concerned a generic application of escitalopram. The suggested indications are identical with those of the originator Ciprale<sup>®</sup> (Lundbeck).

To support the application the Applicant adequately demonstrated bioequivalence between escitalopram Teva and Ciprale<sup>®</sup> (Lundbeck) tablets.

There was no objection against granting the marketing authorization from a clinical point of view.

## **V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The application concerned the generic version of escitalopram 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. This active substance is widely and safely used, the application of the present product does not pose any new risk.

Bioequivalence with the named reference product, already marketed within the European Economic Area more than ten years was duly demonstrated in case of the 10 mg strength. All necessary data supporting the acceptability for the biowaiver for the other strengths were also submitted.

The submitted documentation was formally adequate and scientifically sound. The benefit/risk assessment has been positive.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Escitalopram 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets for the treatment of major depressive episode; treatment of panic disorder with or without agoraphobia; treatment of social anxiety disorder (social phobia); treatment of generalised anxiety disorder; and treatment of obsessive-compulsive disorder is approvable. No objection on behalf of the CMSs was raised against this opinion.

### **V.1. Conditions for the marketing authorisation**

#### *V.1.1 Requirements for specific post-marketing obligations*

Not needed.

#### *V.1.2 Pharmacovigilance system*

The RMS considered that the Detailed Description of Pharmacovigilance System described in the application fulfilled the requirements and provided adequate evidence that the applicant had the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. There was no objection from the CMSs.

#### *V.1.3 Risk Management Plan*

Due to the long lasting use, of escitalopram tablets, the applicant proposed to use the routine pharmacovigilance system as described in Volume 9A of the Notice to Applicants and did not plan to install special risk minimisation measures. The RMS agreed considering that all of the important identified and potential risks discussed during the assessment period are adequately reflected in the SmPC.

#### *V.1.4 Periodic Safety Update Report (PSUR)*

The general PSUR submission cycle of 3 years applies.

#### *V.1.5 Legal status*

Prescription-only medicine.

### **V.2 Summary of Product Characteristics (SmPC)**

The SmPC is, both from pharmaceutical and medical points of view, acceptable but it should be completely harmonised with the originator's.

### **V.3 Package Leaflet and user consultation**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number HU/H/0179/001-004/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Addition of a new, alternative active substance manufacturer with ASMF	II/001	No	17. 02. 2009	29. 08. 2009	approval	no
C.I.2a) Variation submitted for a brand leader update to harmonise information between the originator's product (CipraleX) SmPC/PIL and applicant SmPC/PIL	IB/004	Yes	28. 02. 2011	29. 05. 2011	approval	no
Change in the storage condition of the finished product from „Do not store above 25°C. Store in the original packaging in order to protect from moisture” to „Store below 30°C. Store in the original packaging in order to protect from moisture.”	IB/005	Yes	26. 05. 2011	25. 06. 2011	approval	no
Repeat Use MRP with the CMSs BE, DE, FR, IT, LU, NL, SE and UK	E/001	No	22. 02. 2012	22. 05. 2012	approval	no
Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH to SmPC and PIL <ul style="list-style-type: none"> <li>• SSRI - Risk of impaired male fertility – PhVWP March 2012</li> <li>• Risk of QT prolongation – CMDh/PhVWP/044/2012</li> </ul>	IB/009/G	Yes	17. 10. 2012	16. 11. 2012	approval	no
C.I.3.a variation in line with the commitment made by the Applicant made in the repeat use procedure to submit a variation to bring the PIL and SmPC in line with those of originator's product CipraleX again	IB/011	Yes	24. 09. 2012	15. 03. 2013	approval	no