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Public Assessment Report

Name of the Product:

Amoduo

5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg tablets

(amlodipine besilate/bisoprolol fumarate)

Procedure number: HU/H/0419/001-004/DC

Marketing authorisation holder: Win Medica Pharmaceutical S.A.

Date: 16 December 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg tablets. The holder of the marketing authorisation is Win Medica Pharmaceutical S.A.

The active substances are bisoprolol fumarate/amlodipine besilate.

The Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg tablets contain 5 mg or 10 mg bisoprolol fumarate and 5 mg or 10 mg amlodipine (as amlodipine besilate), respectively.

The other ingredients (excipients) are microcrystalline cellulose (E460), sodium starch glycolate (type A), colloidal anhydrous silica and magnesium stearate (E572).

The appearance of Amoduo tablets is as follows:
- 5 mg/5 mg tablets: white, round, biconvex tablets with bevelled edges (diameter: 6.7–7.1 mm, thickness: 3.0–5.0 mm);
- 10 mg/5 mg tablets: white, oval, biconvex tablets scored on one side (length; 13.0–13.3 mm, width: 8 mm, thickness: 3.4–5.0 mm). The score line is not intended for breaking the tablet;
- 5 mg/10 mg tablets: white, round, slightly biconvex tablets with bevelled edges and engraved with CS on one side (diameter: 10.0–10.2 mm, thickness: 3.4–5.0 mm);
- 10 mg/10 mg tablets: White, round, slightly biconvex tablets with bevelled edges and a score on one side (diameter: 10.0–10.2 mm, thickness: 3.4–5.0 mm). The score line is not intended for breaking the tablet.

The tablets are available in carton boxes in blisters.

Amoduo tablets are indicated for treatment of increased blood pressure and/or heart disease (stable coronary artery disease) in patients already controlled with bisoprolol and amlodipine given concurrently at the same dose level as in the combination.

What patients need to know before taking Amoduo tablets?

Should not take Amoduo tablets those who
- are allergic to bisoprolol, amlodipine, or any of the other ingredients of this medicine, or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing;
- have severe asthma or severe chronic lung disease;
- have severe blood circulation problems in the limbs (such as Raynaud's syndrome), which may cause the fingers and toes to tingle or turn pale or blue;
- have untreated phaeochromocytoma, which is a rare tumour of the adrenal gland;

- have metabolic acidosis, which is a condition when there is too much acid in the blood;
- have acute heart failure;
- have worsening heart failure requiring injection of medicines into a vein, that increase the force of contraction of the heart;
- have slow heart rate;
- have low blood pressure;
- have certain heart conditions causing a very slow heart rate or irregular heartbeat;
- have cardiogenic shock, which is an acute serious, heart condition causing low blood pressure and circulatory failure;
- have narrowing of the aourtic heart valve (aortic stenosis) or cardiogenic shock (a condition where the heart is unable to supply enough blood to the body);
- suffer from heart failure after a heart attack.

Warnings and precautions

Patients who have or have had any of the following conditions should inform their doctor:
- diabetes,
- strict fasting,
- certain heart diseases such as disturbances in heart rhythm, or severe chest pain at rest (Prinzmetal's angina).
- kidney or liver problems,
- less severe blood circulation problems in the limbs,
- less severe asthma or chronic lung disease,
- history of a scaly skin rash (psoriasis),
- tumour of the adrenal gland (phaeochromocytoma),
- thyroid disorder,
- recent heart attack,
- heart failure,
- severe increase in blood pressure (hypertensive crisis).

In addition, the doctor should be informed if the patient is going to have:
- desensitization therapy (for example for the prevention of hay fever), because Amoduo tablets may make it more likely that an allergic reaction is experienced, or such reaction may be more severe;
- anaesthesia (for example for surgery), because Amoduo tablets may influence how the body reacts to this situation.

Children and adolescents

Amoduo tablets are not recommended for use in children or adolescents below the age of 18, because their benefits and risks have not been tested in these age groups.

Other medicines and Amoduo tablets

The following medicines should not be taken with Amoduo tablets without special advice from the doctor:

- certain medicines used to treat high blood pressure, angina pectoris or irregular heart-beat (calcium antagonists such as verapamil and diltiazem);
- certain medicines used to treat high blood pressure such as clonidine, methyldopa, moxonodine, rilmenidine. However, taking these medicines should not be stopped without consulting the doctor first.

Taking the following medicines with Amoduo tablets should also be discussed with the doctor, for Amoduo tablets may affect or be affected by other medicines, or the doctor may need to check the patient's condition more frequently:
- certain medicines used to treat high blood pressure or angina pectoris (dihydropyridine-type calcium antagonists such as felodipine);
- certain medicines used to treat irregular or abnormal heartbeat (Class I antiarrhythmic medicines such as quinidine, disopyramide, lidocaine, phenytoin; flecainide, propafenone);
- certain medicines used to treat irregular or abnormal heartbeat (Class III antiarrhythmic medicines such as amiodarone);
- beta-blockers applied locally (such as timolol eye drops for glaucoma treatment) certain medicines used to treat for example Alzheimer's disease or glaucoma (parasympathomimetics such as tacrine or carbachol) or medicines that are used to treat acute heart problems (sympathomimetics such as isoprenaline and dobutamine);
- antidiabetic medicines including insulin;
- anaesthetic agents (for example during surgery);
- digitalis, used to treat heart failure;
- non-steroidal anti-inflammatory medicines (NSAIDs) used to treat arthritis, pain or inflammation (for example ibuprofen or diclofenac);
- any medicine, which can lower blood pressure as a desired or undesired effect such as antihypertensives, certain medicines for depression (tricyclic antidepressants such as imipramine or amitriptyline), certain medicines used to treat epilepsy or during anaesthesia (barbiturates such as phenobarbital), or certain medicines to treat mental illness characterized by a loss of contact with reality (phenothiazines such as levomepromazine);
- mefloquine, used for prevention or treatment of malaria;
- depression treatment medicines called monoamine oxidase inhibitors (except MAO-B inhibitors) such as moclobemide;
- ketoconazole, itraconazole (anti-fungal medicines);
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV);
- rifampicin, erythromycin, clarithromycin (antibiotics);
- Hypericum perforatum (St. John's Wort);
- verapamil, diltiazem (heart medicines);
- simvastatin (medicine for lowering blood cholesterol).

Amoduo tablets may lower the blood pressure even more if the patient is already taking other medicines to treat high blood pressure.

Pregnancy and breast-feeding

There is a risk that use of Amoduo tablets during pregnancy may harm the baby. Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

The safety of amlodipine in human pregnancy has not been established.

It is not known whether bisoprolol or amlodipine pass into human breast milk. Therefore, breastfeeding is not recommended during therapy with Amoduo tablets.

Driving and using machines

Amoduo tablets may affect the ability to drive or use machines which may be affected depending on how well the patient tolerates the medicine. If the tablets make the patient feel sick, dizzy or tired, or cause a headache, driving and using machines is not recommended and the doctor should be contacted immediately.

How to take Amoduo tablets?

The recommended dose of Amoduo tablets is one tablet per day, taken with some water in the morning, with or without food. The tablets should not be crushed or chewed.

It is important to keep taking the tablets regularly. The patients are encouraged not to wait until the tablets are finished before seeing the doctor.

The score line (if present) is not intended for breaking the tablet.

What to do if more Amoduo tablets wher taken than it should have been?

Having taken more Amoduo tablets than it should have been, the doctor should be consulted immediately. Taking too many tablets may cause the blood pressure to become low or even dangerously low. The patient may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough, even shock can occur. The skin could feel cool and clammy and the patient could lose consciousness. Symptoms of an overdose may also include slowed heart rate, severe difficulty in breathing, or trembling (due to decreased blood sugar).

What to do if taking Amoduo tablets has been forgotten?

There is no reason to worry. If taking a tablet has been forgotten, that dose should be left out completely. The usual dose use be taken next morning. No double dose to make up for a forgotten dose must be taken.

May patients stop taking Amoduo tablets?

The patients should never stop taking Amoduo tablets unless on a doctor’s advice. Their condition may return if stopping using the medicine before advised, or may become much worse.

Possible side effects

Like all medicines, Amoduo tablets can cause side effects, although not everybody experiences them.

The most serious side effects are related to the heart function:
- slowing heart rate (affects more than 1 person in 10);
- worsening heart failure (affects less than 1 person in 10);
- causing slow or irregular heartbeat (affects less than 1 person in 100).

Those who experience any of the following very rare, severe side effects after taking this medicine should visit their doctor:
- sudden wheeziness, chest pain, shortness of breath or difficulty in breathing;
- swelling of eyelids, face or lips;
- swelling of the tongue and throat which causes great difficulty breathing;
- severe skin reactions including intense skin rash, hives, reddening of the skin over the whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions;
- heart attack, abnormal heart beat;
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell.

Those who feel dizzy or weak, or have breathing difficulties must contact their doctor as soon as possible.

Bisoprolol

The following side-effects have been reported.

Common (affects 1 to 10 users in 100):
- dizziness, headache;
- feeling of coldness or numbness in hands or feet;
- stomach or intestine problems such as nausea, vomiting, diarrhoea, or constipation.

Uncommon (affects 1 to 10 users in 1,000):
- sleep disturbances;
- depression;
- slow heart rate;
- low blood pressure;
- breathing problems in patients with asthma or chronic lung disease;
- muscle weakness, muscle cramps;
- tiredness, feeling weak.

Rare (affects 1 to 10 users in 10,000):
- hearing problems;
- allergic runny nose;
- reduced tear flow;
- inflammation of the liver which can cause yellowing of the skin or whites of the eyes;
- certain blood test results for liver function or fat levels differing from normal;
- allergy-like reactions such as itching, flush, rash;
- impaired erection;
- nightmares, hallucinations;
- fainting.

Very rare (affects less than 1 user in 10,000):
- irritation and redness of the eye (conjunctivitis);
- hair loss;
- appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash.

Amlodipine

The following side-effects have been reported.

Common:
- headache, dizziness, sleepiness (especially at the beginning of the treatment);
- flushing;
- abdominal pain, feeling sick (nausea);
- ankle swelling (oedema), tiredness.

Uncommon:
- mood changes, anxiety, depression, sleeplessness;
- palpitations (awareness of your heart beat);
- trembling, taste abnormalities, fainting, weakness;
- numbness or tingling sensation in your limbs; loss of pain sensation;
- visual disturbances, double vision, ringing in the ears;
- low blood pressure;
- sneezing/running nose caused by inflammation of the lining of the nose (rhinitis);
- altered bowel habits, diarrhoea, constipation, indigestion, dry mouth, vomiting (being sick);
- hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration;
- disorder in passing urine, increased need to urinate at night, increased number of times of passing urine;
- inability to obtain an erection; discomfort or enlargement of the breasts in men;
- weakness, pain, feeling unwell;
- joint or muscle pain, muscle cramps, back pain;
- weight increase or decrease.

Rare: confusion.

Very rare:
- decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage);
- excess sugar in blood (hyperglycaemia);
- a disorder of the nerves which can cause weakness, tingling or numbness;
- cough, swelling of the gums;
- abdominal bloating (gastritis);
- abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests;
- increased muscle tension;
- inflammation of blood vessels, often with skin rash;
- sensitivity to light;
- disorders combining rigidity, tremor, and/or movement disorders.

How to store Amoduo tablets?

Do not store them above 30°C. Store in the original package in order to protect from light and moisture.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg tablets. The procedure was finalised at 23 August 2015. 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, 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: Cyprus and Greece) concerned the fixed combinations of amlodipine besilate and bisoprolol fumarate in four strengths, 5mg/5mg, 5mg/10mg, 10mg/5mg and 10mg/10mg. The application has been filed pursuant to Article 8(3) of Directive 2001/83/EC as amended, also based on the Annex I Part II point 7 of the Directive (so-called mixed application).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg tablets from Win Medica Pharmaceutical S.A., Greece.

The combination products are indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease in patients already controlled with amlodipine and bisoprolol given concurrently at the same dose level as in the combination.

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

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the decentralised application of Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg tablets is based on article 8(3) of Directive 2001/83 EC "mixed application".

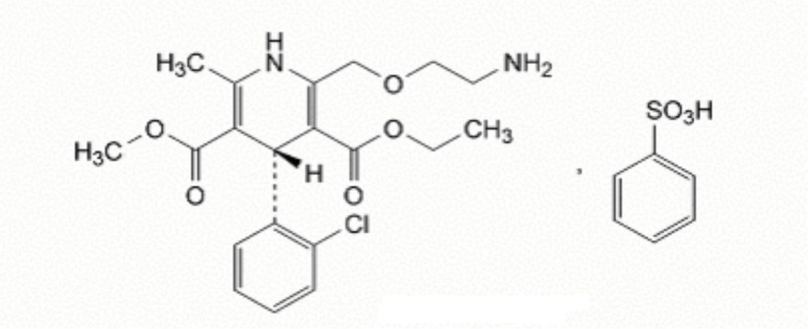
A bioequivalence study has been performed using the products Istin™ 10 mg tablets (amlodipine as besilate) and Concor® 10 mg tablets (bisoprolol fumarate) from the German and British markets, respectively, to support the substitution therapy for treatment of essential hypertension and/or stable coronary artery disease in patients already controlled with amlodipine and bisoprolol given concurrently at the same dose level as in the combination.

II.2 Drug substances

II.2.1 Amlodipine besilate

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: amlodipine besilate
Chemical name: 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Structure:



and enantiomer

The active substance is white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph, with additional tests to show adequate quality.
The Ph. Eur. specification includes the following tests for amlodipine besilate: appearance, solubility, identification (IR), optical rotation, related substances, water content, sulphated ash, assay of amlodipine besilate.

Testing methods not described in details in the Pharmacopoeia 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.

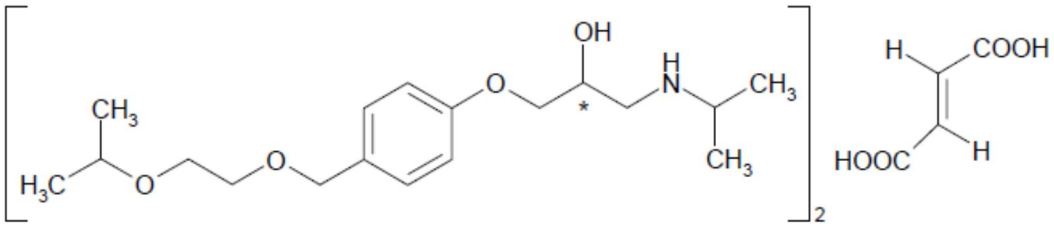
A retest period of 5 years in the packaging material (double polyethylene bag, outer black, in fibre board drum) is indicated on the CEP.

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

II.2.2 Bisoprolol fumarate

Data on the quality and manufacture of the active substance were provided in the submission using the CEP procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: bisoprolol Fumarate
Chemical name: R,S)1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hemifumarate
Structure:



The active substance is white or almost white powder, slightly hygroscopic, very soluble in water and methanol, freely soluble in chloroform, glacial acetic acid and alcohol, slightly sol-

uble in acetone and ethyl acetate. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph, with additional tests to show adequate quality. .

The Ph. Eur. specification includes the following tests for bisoprolol fumarate: appearance, solubility, identification (IR), related substances, water content, sulphated ash, assay of bisoprolol fumarate.

Testing methods not described in details in the Pharmacopoeia 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 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.

A retest period of 2 years in the packaging material (double polyethylene bags (outer black) in triple laminated aluminium pouch (with desiccant in between) placed in a fibre board drum) is indicated on the CEPs.

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

II.3 Medicinal product

The aim was to develop a combination drug formulations (fixed dose combinations) of amlodipine/bisoprolol tablets as substitution therapy of mono products Istin™ tablets (amlodipine besilate; Pfizer) and Concor® (bisoprolol fumarate; MSD).

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

As regards dissolution and impurity profile the products are shown to be similar to the reference products.

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 description of bisoprolol fumarate/amlodipine besilate tablets per strength are as follows:
- 5 mg/5 mg tablet: white, round biconvex tablets with bevelled edges. Tablet diameter: -6.7[šu1]-7.1 mm, thickness: 3.0-5.0 mm.
- 10 mg/5 mg tablet: white, oval, biconvex tablets scored on one side. Tablet length; 13.0-13.3 mm, width: 8 mm, thickness: 3.4-5.0 mm.

- 5 mg/10 mg tablet: white, round, slightly biconvex tablets with bevelled edges, engraved with CS on one side. Tablet diameter: 10.0-10.2 mm, thickness: 3.4-5.0 mm.
- 10 mg/10 mg tablet: white, round, slightly biconvex tablets scored on one side and with bevelled edges. Tablet diameter: 10.0-10.2 mm, thickness: 3.4-5.0 mm.

The excipients used in the finished products are microcrystalline cellulose, sodium starch glycolate type A, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the Ph. Eur. general monograph 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 International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blisters and box. 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 24 months with the storage condition “store below 30°C in original package in order to protect from moisture and light” is approved.

The Summary of Product Characteristics, patient information (package) leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their 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 quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both amlodipine and bisoprolol are well known.

Claiming that both drugs are widely used well-known active substances the applicant has not performed further non-clinical studies. The overview is based on literature review.

The applicant has found no preclinical data regarding the pharmacokinetic interactions between bisoprolol and amlodipine.

According to Article 8(3) of the Directive 2001/83/EC the product dossier should be full; e.g. data of the full preclinical and clinical development must be provided. However, the Directive allows the mixed application when the dossier contains both literature data and results of preclinical and clinical studies performed by the applicants. The authorities can decide whether the own data provided is sufficient to grant the marketing authorization. Taking into account that both compounds are widely used in the treatment of hypertension and/or chronic stable angina and the product is intended for substitution therapy only – meaning that neither first nor second line indications are clamed – the literature data are sufficient from a non-clinical point of view.

III.2 Pharmacology

Amlodipine is an effective and potent calcium antagonist. When compared to other 1,4-dihydropyridines, the inhibition of L-type Ca^{2+} channels by amlodipine was concentration dependent and increased gradually. It was reported that the association and dissociation constants for the interaction of amlodipine with receptors is 2-3 orders of magnitude lower than that for other dihydropyridines. This specific interaction of amlodipine with membranes is believed to correlate with drug's distinctive pharmacodynamic and pharmacokinetic activities.

The drug was shown to have a gradual onset and sustained antihypertensive action in vivo. In vivo pharmacodynamic studies with amlodipine, performed in several animal models of hypertension, after single or repeated administration, either by intravenous or oral route, demonstrated effective antihypertensive action of the drug substance. In addition to amlodipine's antihypertensive action, the drug substance demonstrated to have antiatherosclerotic effects, beneficial effects on renal function as well as cardio protective effects. In mentioned studies, no differences among amlodipine salts used in mentioned studies were recorded.

Studies, in which evaluation of secondary pharmacodynamic effects were evaluated, demonstrated that amlodipine possessed certain analgesic properties and has beneficial effects in the treatment of experimentally-induced diabetes. In vitro studies showed evidence that amlodipine inhibits a number of different cytochrome P-450 forms and therefore has a potential to

inhibit metabolism of a large number of drugs. Safety pharmacology studies showed that adverse effects on cardiovascular, respiratory and central nervous system could occur when amlodipine was given at very high dosage. Cardiovascular side-effects were reported in dogs, which seemed to be especially sensitive to the toxic action of amlodipine.

The adverse effect on respiration was noted in rodents, but not in cats, only after intravenous administration of amlodipine. Amlodipine is poorly transported through the blood-brain barrier and its' action on the central nervous system could be demonstrated in laboratory animals only if very high doses were administered. Co-administration of amlodipine with other drugs did not revealed evidence of pharmacodynamic drug interactions that could significantly influence the therapeutic action.

Bisoprolol is a cardio selective adrenoceptor blocking agent without significant membrane stabilizing or intrinsic sympathomimetic activities in its therapeutic dose range. At higher doses bisoprolol also inhibits β_2-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose. In comparison with other β_1-selective blockers (atenolol, metoprolol, betaxolol) bisoprolol proved to be the compound with the highest β_1-selectivity in all in vitro and in vivo experiments and in all animal species investigated. The mechanism of action of its antihypertensive effects has not been completely established. Factors which may be involved include: decreased cardiac output, inhibition of renin release by the kidneys and diminution of tonic sympathetic outflow from the vasomotor centres in the brain.

Amlodipine/bisoprolol combination: the applicant has not conducted any combination study in animals. Since there are no overlapping target organs, toxic effects or unwanted pharmacodynamic effects in the toxicology and safety pharmacology profiles of the individual compounds, moreover the preclinical safety studies indicate a wide therapeutic range compared to the recommended human dose, lack of specific preclinical safety studies on the combination of the two compounds could be considered justified.

III.3 Pharmacokinetics

Amlodipine: pharmacokinetic studies performed in laboratory animals revealed that amlodipine is rapidly absorbed after oral administration and that the peak plasma levels were obtained 2-7 h after dosing. These pharmacokinetic properties correlated well with the pharmacodynamic action. The drug substance is widely distributed within the body tissues and extensively bound to plasma proteins. Metabolism studies indicated extensive biotransformation of the drug to numerous metabolites without significant calcium antagonistic activity. Determination of plasma levels seemed to be a reasonable comparative measure of systemic exposure between animal species used in safety evaluation and man.

Bisoprolol: in three animal species (rat, dog, and monkey), bisoprolol-^{14}C was well absorbed from the gastrointestinal tract, since, irrespective of the route of administration (p.o. or i.v.), 70-90% of the ^{14}C-dose was recovered in the urine. Animal studies using rats have shown that bisoprolol is rapidly and widely distributed.

The hepatic metabolism of bisoprolol was similar in animals (rats, dogs, monkeys) and humans and consisted of O-dealkylation followed by oxidation to 3 carboxylic acid metabolites; direct pharmacological testing and indirect subtype selective p-adrenoceptor assays have shown that the 3 metabolites are devoid of β-adrenoceptor antagonistic activity in man.

After both i.v. and oral administration of bisoprolol in dogs, the geometric mean elimination half-life was approximately 4 hours, and the mean residence time of the bisoprolol molecules within the body was calculated to be 6 hours.

In conclusion, bisoprolol is a well-tolerated and effective antihypertensive agent which demonstrates beneficial outcomes in animal models of hypertension and cardiac failure.

III.4 Toxicology

Amlodipine: single dose administration of both amlodipine besilate and maleate salts in rats results in a moderate toxicity after oral dosing. The LD_{50} values were between 100 and 700 mg/kg.

Results of repeat-dose toxicity studies revealed evidence that body weight gain was altered when either besilate or maleate salt of amlodipine were administered orally in rats at doses between 15 and ≥30 mg/kg/day. Higher doses needed shorter time of dosing to suppress weight gain that did lower ones. Similarly, mortality was registered at doses higher than 20 mg/kg/day when the drug substance was administered for 1 month or more, and no differences were noted among two amlodipine salts. Diuretic effect of amlodipine was registered already at 10 mg/kg/day dose, and changes of some clinical biochemistry parameters indicated altered renal (8 and 16 mg/kg/day for 1 month) and liver (30 mg/kg/day for 2 week, 15 mg/kg for 3 months) function without significant histopathological findings. The most prominent drug-related finding in rats was enlargement of the zona granulosa of the adrenal gland. This toxic effect was noted in animals administered the drug substance at doses 5 to 25 mg/kg/day for 2 months to 1 year regardless of amlodipine salt used.

The No-Observed-Effect-Level (NOEL) for amlodipine maleate in rats, determined in repeat dose toxicity studies was between 3 and 10 mg/kg/day, while NOEL for amlodipine besilate was between 2 and 3 mg/kg/day. In general NOEL was reversely proportional to the treatment duration.

Dogs seemed to be more sensitive to the toxic action of amlodipine than rats. Repeated administration of the drug substance (studies were performed only with maleate salt) caused lesions of the right atria. These lesions occurred only when treatment duration exceeded 6 months and administered doses increased to up to 7-times maximal human daily dosage.

Genotoxicity potential of both amlodipine salts was evaluated in a whole battery of in vitro and in vivo assays. Results of these studies revealed evidence that amlodipine is not mutagenic.

Fertility studies in male and female rats indicated no adverse effects on the reproductive function, although recently published paper indicated that amlodipine besilate could alter male reproductive function if administered to young rats. Amlodipine was not embryotoxic, fetotoxic or teratogenic in rats and rabbits and did not influence postnatal development of offsprings. The drug substance was found to prolong the length of gestation and cause difficulties in littering in rats at doses 50 times the maximum recommended human dose.

Bisoprolol: on oral administration the LD_{50} was 734 for the mouse and 1116 mg/kg for the rat with a follow-up period of 14 days. On intravenous administration values of 127 (mouse), 53 (rat) and 24 (dog) mg/kg were found.

In repeat dose toxicology studies daily i.v. administration of 0.2, 1 and 5 mg/kg in rats and 1, 3 and 10 mg/kg bisoprolol in dogs was tolerated for four weeks with no sign of significant toxicological changes. No toxic effects were detected in rats after oral administration for 6 months at daily doses of 15, 50 and 150 mg/kg. 10 mg/kg was not toxic for beagles after daily administration for 6 months. Rats tolerated daily treatment with 25 mg/kg for 12 months with no toxic damage. 75 mg/kg was also tolerated, with the exception of a slight reduction in body weight gain. In a 12-month study in beagles daily doses of 3, 10 and 30 mg/kg were tolerated.

The toxicological studies revealed no irreversible organ damage by bisoprolol. In animal experiments bisoprolol was not cytotoxic nor mutagenic. Although it was embryo toxic at higher doses it was not teratogenic nor was it carcinogenic in the mouse or rat.

III.5 Ecotoxicology/environmental risk assessment (ERA)

These combination products are indicated for a substitution indication and as such it will replace the use of the co-administered monocomponent products. Thus, the exposure of the environment to amlodipine and bisoprolol will not increase by the use of these products. Consequently, no environmental risk assessment deemed necessary.

III.6 Discussion on the non-clinical aspects

The application is based on Article 8(3) of Directive 2001/83/EC, and on the Annex I Part II point 7 of Article 8(3) of Directive 2001/83/EC, i.e. it is a so-called mixed application.. Pharmacodynamics, pharmacokinetics and toxicology of both amlodipine and bisoprolol are well-known. As the combination is only for substitution therapy there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The justification for a combination of amlodipine and bisoprolol is based on their synergistic effects on several physiopathologic mechanisms. The combination is intended for use as a substitution in patients suffering from hypertension and stable coronary artery disease. The application is submitted according to Article 8(3) of Directive 2001/83/EC as amended. The application is also based on the Annex I Part II point 7 of Article 8(3) of Directive 2001/83/EC (so-called mixed application).

> This section states the following: "Mixed marketing authorisation applications shall mean marketing authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis."

Both active substances are well-known.

The applicant has followed the recommendations laid in the *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev. 1, London, 19 February 2009). The *Guideline on the non-clinical development of fixed combinations of medicinal products* (EMEA/CHMP/SWP/258498/2005) and *Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention* (CHMP/EWP/191583/2005) have also been followed.

To support the application the applicant has submitted one bioequivalence study conducted in accordance with the *Guideline on the Investigation of Bioequivalence* (CHMP/EWP/QWP/1401/98/Rev.1).

IV.2 Pharmacokinetics

IV.2.1 Literature data

Amlodipine is slowly but almost completely absorbed from the human gastrointestinal tract. Oral bioavailability of amlodipine ranges from 52 to 88%, with the mean of 64%. After oral doses of 2.5, 5, and 10 mg, linear and age-independent relationships were observed between the dose and both AUC and C_{max}. Time to C_{max} (t_{max}) after oral administration was ranging from 6 to 12 h. Absorption of amlodipine is unaffected by food, peak concentration, time to peak concentration, plasma half-life and area under the plasma concentration curve (AUC) were not significantly different between fed and fasting state.

The mean volume of distribution (V_d) after a single dose intravenous application of amlodipine was 21 l/kg indicating that a large proportion of the body load of drug is in the tissues rather than in the blood. Amlodipine is highly protein bound with more than 95 %.

Amlodipine is slowly but extensively (about 90%) metabolised in the liver with possible involvement of CYP3A activity, therefore caution is advised when amlodipine is administered concomitantly with CYP3A inducers or inhibitors. Only 4-5% of unchanged drug recovered in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Amlodipine has no active metabolites.

Bisoprolol is absorbed almost completely (> 90%) from the gastrointestinal tract. Due to the very small first pass effect (approx. 10%), its absolute bioavailability is approximately 90% after oral administration. Its distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites, which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in a non-metabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with mild to moderate liver function impairment or renal insufficiency. Total clearance is approximately 15 l/h. The elimination half-life in plasma is 10-12 hours. The kinetics of bisoprolol are linear between 5 and 20 mg and independent of age.

Amlodipine/bisoprolol combination: according to the literature data the two compounds do not interact in the pharmacokinetic processes.

IV.2.2 Bioequivalence study

The clinical development performed by the applicant comprised of an open-label, single-dose, two-way, crossover study, during which the subjects received the fixed dose combination of amlodipine/bisoprolol hemifumarate 10 mg/10 mg and co-administration of amlodipine 10 mg (Istin™, Pfizer, Germany) and bisoprolol hemifumarate 10 mg (Concor® Merck KG, Germany) as separate tablets in healthy male volunteers under fasting conditions.

Determination of both bisoprolol and amlodipine in plasma samples was performed using validated LC/MS/MS methods.

The applicant stated that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Pharmacokinetic parameters AUC_t, AUC_i, R_{AUC} (residual area), C_{max}, T_{max}, T_{half}, and K_{el} of bisoprolol and pharmacokinetic parameters AUC_{0-72}, C_{max}, T_{max} of amlodipine were determined from individual plasma concentration *vs* time profiles.

The calculated pharmacokinetic parameters of bisoprolol and amlodipine were used for the subsequent average evaluation that consisted of the following procedures:

- analysis of variance taking into account sequence, subject within sequence, formulation and period was performed on the ln transformed AUC_t, AUC_i and C_{max} parameters of bisoprolol and C_{max}, AUC_{0-72} parameters of amlodipine using the SAS® System GLM procedure;
- the bioequivalence between the test formulation *vs*. reference formulation was tested by the 90 % (shortest) confidence intervals of parameters, which is equivalent to the Schuirmann's two one-sided *t* tests. Confidence intervals were determined for the ln-transformed AUC_t, AUC_i, and C_{max} parameters of bisoprolol and C_{max}, AUC_{0-72} parameters of amlodipine using the formulations least squares means (LS-Means) and the residual values obtained from ANOVA. Point estimates for the ratio of average bioavailability (maximum likelihood estimators) were also determined for the above mentioned parameters on the basis of the calculated LS-Means;
- for the T_{max} parameter the nonparametric test was applied.

Bioequivalence was concluded if the 90% CIs for the ratio (test/reference) of the means of C_{max}, AUC_t, parameters of bisoprolol and AUC_{0-72} and C_{max} AUC_{0-72} parameters of amlodipine were included within interval 80-125%.

The results are shown below.

Parameter	Ratio Test/Reference	Confidence interval
Amlodipine		
AUC_{0-72h}	106.14%	102.51% – 109.89%
C_{max}	106.33%	102.35% – 110-45%
Bisoprolol		
AUC_t	100.10%	97.57% – 102.69%
C_{max}	104.63%	100.26% – 109.19%

The 90% confidence intervals of the ratios of LS-Means derived from analysis on the ln-transformed PK parameters AUC_t and C_{max} for bisoprolol and AUC_{0-72} and C_{max} for amlodipine were within the 80.00-125.00% acceptance range.

Conclusion on the bioequivalence study

Based on these results, the bisoprolol hemifumarate/amlodipine 10/10mg tablets (Test) and co-administered Concor® 10 mg film-coated tablets (bisoprolol fumarate, Merck KG, Germany) and Istin™ 10 mg tablets (amlodipine besilate, Pfizer Limited, UK) (Reference) are bioequivalent under fasting conditions.

Biowaiver

The results of bioequivalence study with amlodipine / bisoprolol 10/10 mg strength can be extrapolated to other strengths: 5/5 mg, 10/5 mg and 5/10 mg according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

The pharmacodynamics of *amlodipine* is well established. It belongs to the dihydropiridine Ca^{++}-channel blockers. It inhibits the calcium influx through the L-type (slow) Ca^{++}-channels. As calcium is an essential mediator of smooth muscle contraction amlodipine relaxes smooth muscles especially the blood vessels. By this vasodilating effect amlodipine reduces the peripheral vascular resistance this way it reduces blood pressure and the afterload for the heart as well. By decreasing afterload it reduces the oxygen demand of the heart. Furthermore, dilation of coronary arteries improves the cardiac oxygen supply. These two latter mechanisms may result in preventing angina attacks in chronic stable angina as well as in Prinzmetal's angina (coronary spasm). Despite its marked vasodilatory effect it does not cause strong reflex tachycardia. The negative inotropic effect of amlodipine on the heart is weak provided by its good vasoselectivity over the cardiac L-type channels.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of its administration.

In patients with angina, by once daily administration it increases total exercise time, time to angina onset, and time to significant ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma. It has not been associated with any adverse metabolic effects: it had no effect on the level of plasma lipids, blood glucose and serum uric acid and it was suitable for use in patients with asthma

Bisoprolol is a potent, highly β_1-selective adrenoreceptor-blocking agent devoid of intrinsic sympathomimetic activity (ISA) and without relevant membrane stabilising activity. It only shows low affinity to the β_2-receptor of the smooth muscles of bronchi and vessels as well as to the β_2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β_2-mediated metabolic effects. Its β_1-selectivity extends beyond the therapeutic dose range. Bisoprolol has no explicit negative inotropic effect.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Antihypertensive effect of beta-blockers is among others due to decrease of renin activity.

Bisoprolol has its maximal effect 3-4 hours after oral administration.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

It usually exerts its maximal antihypertensive effect after 2 weeks.

Amlodipine and bisoprolol combination: the justification for a combination of amlodipine and bisoprolol is based on their synergistic effects in their antihypertensive and antianginal mechanisms. The combination tablet may provide a better compliance of the patients than the separate pills. To justify the wide therapeutic experience with the concomitant use of bisoprolol and amlodipine, the IMS MIDAS standardized international medical information from five European markets were analysed; the data from 2009, 2010 and 2011 have been collected. The applicant has provided detailed co-prescription data with amlodipine and bisoprolol from Hungary and from the concerned member states. The co-prescription tendency is increasing year by year. The co-prescription data from Hungary have been separated according to the claimed indications.

IV.4 Clinical efficacy

The applicant has not performed therapeutic clinical trials. As the combination is solely for substitution therapy according to the CHMP/EWP/191583/2005 *Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention* pharmacodynamic studies are not required. However, literature references should adequately justify the combination use in the desired indications.

Regarding hypertension, the Clinical Overview summarizes the data of two clinical trials with bisoprolol and amlodipine combinations. In one trial only the antihypertensive effect of the combination was measured without monocomponent control. The combination was well-tolerated and efficient. The lack of control rules out any firm conclusion of an additional benefit when the two compounds are used in combination. The other study compared the safety profile of amlodipine monotherapy and amlodipine/bisoprolol combination. The combination was well-tolerated and the response rate and efficiency was better than in the amlodipine arm. Other studies compared bisoprolol with Ca^{++}-channel blockers and amlodipine with beta-blockers and supported the better antihypertensive effect of the combination of beta-blockers and Ca^{++}-channel blockers. The applicant has provided further data from three meta-analyses regarding the use of bisoprolol for hypertension. The vast data of the benefit of both com-

pounds in hypertensive patients and the co-prescription numbers support the need of the all four combination pills for hypertension.

Regarding angina pectoris the literature data are scarcer. The applicant has found only one study with bisoprolol/amlodipine combination in angina pectoris and the study resulted in no additional benefit with the combination compared to the monocomponent treated patients. The co-prescription data obtained from the Hungarian market show that approximately 10-11% of the co-prescription of amlodipine and bisoprolol was intended to treat chronic ischaemic heart disease/angina pectoris. The applicant's argument that these conditions most likely cover chronic stable angina is acceptable. The applicant refers to clinical cardiology guidelines in order to justify the need of co-administration of amlodipine and bisoprolol. It is acknowledged that these guidelines recommend using dihydropiridines and beta-blockers together for chronic stable angina, however, from a regulatory point of view these information can only support the evidence obtained from clinical studies. Furthermore, the recommendations do not specify exactly which active substances can be combined and group-effect cannot be considered to establish an indication. Nevertheless the combination is only for substitution indication therefore the decision to combine amlodipine and bisoprolol is made exclusively by the prescriber doctor. The applicant has provided four more references to support bisoprolol use for chronic stable angina. Additionally, the data about the combination of amlodipine and other beta-blockers support this indication. New clinical studies specifically designed to investigate the effects of amlodipine and bisoprolol combination in coronary artery disease are not available (the only study has been include in the Clinical Overview of the initial application). Therefore, the substitution indication of amlodipine/bisoprolol for stable coronary artery disease has also been accepted.

IV.5 Clinical safety

The clinical safety of both bisoprolol and amlodipine is well-know. The literature review has not identified any specific new risk due to the combination of the active substances either on pharmacodynamic or pharmacokinetic grounds.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

The summary of safety concerns is shown in the next Table.

Summary of safety concerns	
Important identified risks	Cardiac disorders: myocardial infarction, cardiac failure, worsening of heart failure, arrhythmias Hypotension Hypersensitivity reactions Bronchospasm Syncope Toxic skin reactions Hepatobiliary disorders Interactions with class IV antiarrhythmic and class I antiarrhythmic drugs Interactions with strong or moderate CYP3A4 inhibitors
Important potential risks	Parkinsonism and Parkinson's disease Interstitial lung disease Hyperkalaemia Torsade de pointes Hypoglycaemia and blood glucose level decreased Interstitial pneumonitis Pulmonary fibrosis Retroperitoneal fibrosis Peyronie's disease Elevated ANA and lupus diseases Renal failure Attempted/completed suicide and suicide ideation Interaction between bisoprolol and monoamine oxidase inhibitors Interaction between bisoprolol and ergotamine derivatives Medication errors including overdose Off label use
Missing information	Use in patients with hepatic impairment The use by breast feeding women

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to products of Win Medica Pharmaceutical S.A. of bisoprolol-amlodipin 5 mg/5 mg, 10 mg/5 mg, 5 mg/10mg and 10 mg/10 mg tablets. No additional activities are proposed.

Risk minimisation measures: routine measures (i.e. wording in the SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to these tablets. No additional activities are proposed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

This stand-alone, full mixed application concerns fixed combinations of amlodipine and bisoprolol. The requested indication is substitution therapy for patients suffering from hypertension and stable coronary artery disease already adequately controlled with monocomponent containing tablets given concurrently.

To support the application the applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time and thoroughly reviewed the scientific literature. For further justification the applicant has provided co-prescription data from the markets of the concerned member states.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

This application concerns fixed combinations of amlodipine and bisoprolol. The requested indication is substitution therapy for patients suffering from hypertension and stable coronary artery disease already adequately controlled with monocomponent containing tablets given concurrently.

The applicant has adequately demonstrated bioequivalence between the combination and the monocomponent originators given at the same time and thoroughly reviewed the scientific literature. For further justification the applicant has provided co-prescription data from the markets of the concerned member states.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Amoduo 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg and 10 mg/10 mg tablets from Win Medica Pharmaceutical S.A., Greece.

V.2 Classification

Prescription-only medicine.

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 patient information leaflet 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	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached