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Public Assessment Report

Name of the Product:

Stacapolo

**50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg,
150 mg/37.5 mg/200 mg, 200 mg/50 mg/200 mg
film-coated tablets**

(levodopa/carbidopa/entacapone)

Procedure number: HU/H/0363/001-004/DC

Marketing authorisation holder: Vipharm S.A.

Date: 17 March 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of Stacapolo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg and 200 mg/50 mg/200 mg film-coated tablets. The holder of the marketing authorisation is Vipharm S.A.

Stacapolo contains three active substances (levodopa, carbidopa and entacapone) in one film-coated tablet. Stacapolo is used for the treatment of Parkinson's disease.

Parkinson's disease is caused by low levels of a substance called dopamine in the brain. Levodopa increases the amount of dopamine and hence reduces the symptoms of Parkinson's disease. Carbidopa and entacapone improve the antiparkinson effects of levodopa.

The other ingredients in the tablet cores are croscarmellose sodium, hydroxypropylcellulose, trehalose dihydrate, cellulose, sodium sulphate, cellulose microcrystalline and magnesium stearate.

The ingredients in the film-coating are polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol 3350 (E1521), red iron dioxide (E172), lecithin (soya) (E322) and yellow iron oxide (E172).

Stacapolo film-coated tablets are brownish red, oval, biconvex, unscored marked with
- the 50 mg/12.5 mg/200 mg strength: "50" on one side and "LEC" on the opposite side;
- the 100 mg/25 mg/200 mg strength: "100" on one side and "LEC" on the opposite side;
- the 150 mg/37.5 mg/200 mg strength: "150" on one side and "LEC" on the opposite side;
- the 200 mg/50 mg/200 mg strength: "200" on one side and "LEC" on the opposite side.

What patients need to know before taking Stacapolo

Stacapolo should not be taken by patients who
- are allergic to levodopa, carbidopa or entacapone, or any of the other ingredients of this medicine,
- have narrow-angle glaucoma (an eye disorder),
- have a tumour of the adrenal gland,
- are taking certain medicines for treating depression (combinations of selective MAO-A and MAO-B inhibitors, or non-selective MAO-inhibitors),
- have ever had neuroleptic malignant syndrome (NMS – this is a rare reaction to medicines used to treat severe mental disorders),
- have ever had non-traumatic rhabdomyolysis (a rare muscle disorder),
- have a severe liver disease.

Stacapolo contains lecithin (soya). Those who are allergic to peanut or soya, do not use this medicinal product.

Warnings and precautions

Those who have or have ever had any of the following conditions talk to their doctor before taking Stacapolo:
- a heart attack or any other diseases of the heart including cardiac arrhythmias, or of the blood
  vessels,
- asthma or any other disease of the lungs,
- a liver problem, because the dose may need to be adjusted,
- kidney or hormone-related diseases,
- stomach ulcers or convulsions,
- experiencing prolonged diarrhoea as it may be a sign of inflammation of the colon,
- any form of severe mental disorder like psychosis,
- chronic wide-angle glaucoma, because the dose may need to be adjusted and the pressure in the eyes may need to be monitored.

Those who are currently taking any of the following medicines should also consult their doctor:
- antipsychotics (medicines used to treat psychosis),
- a medicine which may cause low blood pressure when rising from a chair or bed (for Stacapolo may make these reactions worse).

Those who, during the treatment with Stacapolo, experience any of the following:
- the muscles get very rigid or jerk violently, or if getting tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in the blood pressure. (If any of this happens, the doctor should be contacted immediately!),
- feeling depressed, having suicidal thoughts, or noticing unusual changes in the behaviour,
- finding themselves suddenly falling asleep, or if feeling very drowsy. If this happens, the patient should not drive or use any tools or machines (see also section 'Driving and using machines'),
- noticing that uncontrolled movements begin or get worse after starting to take Stacapolo. If this happens, the doctor may need to change the dose of the antiparkinson medicine,
- experiencing diarrhoea: monitoring of the weight is recommended in order to avoid potentially excessive weight loss,
- experiencing progressive anorexia, asthenia (weakness, exhaustion) and weight decrease within a relatively short period of time. If this happens, a general medical evaluation including liver function should be considered,
- feeling the need to stop using Stacapolo.

The patient should consult the doctor if he/she or his/her family/carer notices developing urges or cravings to behave in ways that are unusual for him/her or the patient cannot resist the impulse, drive or temptation to carry out certain activities that could harm himself/herself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. The doctor may need to review the treatments.

The doctor may take some regular laboratory tests during a long term treatment with Stacapolo.

Those who must undergo surgery, should tell their doctor that they are using Stacapolo.

Stacapolo is not recommended to be used for treatment of extrapyramidal symptoms (e.g. involuntary movements, shaking, muscle rigidity and muscle contractions) caused by other medicines.

Children and adolescents

Experience with Stacapolo in patients under 18 years is limited. Therefore, the use of Stacapolo in children and adolescents is not recommended.

Other medicines and Stacapolo

Whenever the patient is taking, has recently taken or might take any other medicines, the doctor should be consulted.

Stacapolo should not be used if the patient is taking certain medicines for treating depression (combinations of selective MAO-A and MAO-B inhibitors, or non-selective MAO inhibitors). Stacapolo may increase the effects and side effects of such medicines. These include:
- medicines used to treat depression such as moclobemide, amitryptiline, desipramine, maprotiline, venlafaxine and paroxetine,
- rimiterole and isoprenaline, used to treat respiratory diseases,
- adrenaline, used for severe allergic reactions,
- noradrenaline, dopamine and dobutamine, used to treat heart diseases and low blood pressure,
- alpha-methyldopa, used to treat high blood pressure,
- apomorphine, which is used to treat Parkinson's disease.

The effects of Stacapolo may be weakened by certain medicines. These include:
- dopamine antagonists used to treat mental disorders, nausea and vomiting,
- phenytoin, used to prevent convulsions,
- papaverine used to relax the muscles.

Stacapolo may make it harder to digest iron. Therefore, Stacapolo and iron supplements should not be taken at the same time. After taking one of them, the patient should wait at least 2 to 3 hours before taking the other.

Stacapolo with food and drink

Stacapolo may be taken with or without food. For some patients, Stacapolo may not be well absorbed if it is taken with, or shortly after eating protein-rich food (such as meats, fish, dairy products, seeds and nuts). Those to whom this may apply should consult their doctor.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their your doctor for advice before taking this medicine.

During treatment with Stacapolo breast-feeding should be stopped.

Driving and using machines

Stacapolo may lower the blood pressure, which may make the patients feel light-headed or dizzy. Therefore, they should be particularly careful when driving or using any tools or machines.

Those who feel very drowsy, or sometimes find themselves suddenly falling asleep, wait until feeling fully awaken again before driving or doing anything else that requires to be alert. Otherwise, patients may put themselves and others at risk of serious injury or death.

Stacapolo contains lecithin (soya).

Those who are allergic to peanut or soya, do not use this medicinal product.

How to take Stacapolo

For adults and elderly the following rules apply.
- The doctor will tell exactly how many tablets of Stacapolo to take each day.
- The tablets are not intended to be split or broken into smaller pieces.
- The patient should take only one tablet each time.
- Depending on how the patient respond to treatment, the doctor may suggest a higher or lower dose.
- Those who take Stacapolo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, or 150 mg/37.5 mg/200 mg tablets, do not take more than 10 tablets per day.
- Those who take Stacapolo 200 mg/50 mg/200 mg, do not take more than 7 tablets of this strength per day.

What to do if taken more Stacapolo than prescribed?

If accidentally more Stacapolo tablets have been taken than it should be, the doctor or a pharmacist should be contacted immediately. In case of an overdose the patient may feel confused or agitated, the heart rate may be slower or faster than normal or the colour of the skin, tongue, eyes or urine may change.

What to do if taking Stacapolo is forgotten?

The patient should not take a double dose to make up for a forgotten tablet.

If it is more than 1 hour until the next dose: one tablet should be taken as soon as the patient remembers, and the next tablet at the normal time.

If it is less than 1 hour until the next dose: the tablet should be taken as soon as the patient remembers, wait 1 hour, then take another tablet. After that carry on as normal.

Always leave at least an hour between Stacapolo tablets, to avoid possible side effects.

May taking Stacapolo be stopped?

Patients should not stop taking Stacapolo because of the doctor's order. In such a case the doctor may need to adjust the other antiparkinson medicines, especially levodopa, to give sufficient control of the symptoms. If one suddenly stops taking Stacapolo and other antiparkinsonian medicines it may result in unwanted side effects.

Possible side effects

Like all medicines, Stacapolo can also cause side effects, although not everybody experiences them. Many of the side effects can be relieved by adjusting the dose.

If during the treatment with Stacapolo experience the following symptoms are experienced, the doctor should be contacted immediately:
- the muscles get very rigid or jerk violently, the patient feels tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in the blood pressure. These can be symptoms of neuroleptic malignant syndrome (NMS, a rare severe reaction to medicines used to treat disorders of the central nervous system) or rhabdomyolysis (a rare severe muscle disorder);
- allergic reaction, the signs may include hives (nettle rash), itching, rash, swelling of the face, lips, tongue or throat. This may cause difficulties in breathing or swallowing.

Other side effects are as follows.

Very common (may affect more than 1 in 10 people):
- uncontrolled movements (dyskinesias),
- feeling sick (nausea),
- harmless reddish-brown discoloration of urine,
- muscle pain,
- diarrhoea.

Common (may affect up to 1 in 10 people):
- light-headedness or fainting due to low blood pressure, high blood pressure,
- worsening of Parkinson`s symptoms, dizziness, drowsiness,
- vomiting, abdominal pain and discomfort, heartburn, dry mouth, constipation,
- inability to sleep, hallucinations, confusion, abnormal dreams (including nightmares), tiredness,
- mental changes including problems with memory, anxiety and depression (possibly with thoughts of suicide),
- heart or artery disease events (e.g. chest pain), irregular heart rate or rhythm,

- more frequent falling,
- shortness of breath,
- increased sweating, rashes,
- muscle cramps, swelling of legs,
- blurred vision,
- anaemia,
- decreased appetite, decreased weight,
- headache, joint pain,
- urinary tract infection.

Uncommon (may affect up to 1 in 100 people):
- heart attack,
- bleeding in the gut,
- changes in the blood cell count which may result in bleeding, abnormal liver function test results,
- convulsions,
- feeling agitated,
- psychotic symptoms,
- colitis (inflammation of the colon),
- discolouration other than urine (e.g. skin, nail, hair, sweat),
- swallowing difficulties,
- inability to urinate.

The following side effects have also been reported:
- hepatitis (inflammation of the liver),
- itching.

Patients may also experience the following side effects: inability to resist the impulse to perform an action that could be harmful, which may include:
- strong impulse to gamble excessively, despite serious or personal family consequences,
- altered or increased sexual interest and behaviour of significant concern to themselves or to others, for example, an increased sexual drive,
- uncontrollable excessive shopping or spending,
- binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy the hunger).

Those who experience any of these behaviours should consult their doctor; they will discuss ways of managing or reducing the symptoms.

How to store Stacapolo

This medicinal product does not require any special storage conditions but keep it out of the sight and reach of children.

Scientific discussion

This module reflects the scientific discussion for the approval of Stacapolo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg and 200 mg/50 mg/200 mg film-coated tablets. The procedure was finalised at 18 December 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: the Czech Republic and the Slovak Republic) concerns the fixed combination of levodopa/carbidopa/entacapone film-coated tablets in four strengths, 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg and 200 mg/50 mg/200 mg. The application has been submitted according to Article 10(1) of Directive 2001/83/EC as amended (so-called generic application).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Stacapolo film-coated tablets 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 200 mg/50 mg/200 mg levodopa/carbidopa/entacapone. The holder of the marketing authorization is Vipharm S.A., Poland.

The products are indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC and therefore no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product and reference products in two studies.

The reference (originator) products were Stalevo 50mg/12.5mg/200mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 and 200 mg/50 mg/200 mg film-coated tablets by Orion Corporation, approved for more than 10 years in the European Economic Area.

The product development rationale as outlined by the applicant is primarily related to the benefits of fixed combination therapy that contains entacapone as a reversible COMT inhibitor in addition to L-DOPA and carbidopa. According to the current understanding, the symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Dopamine does not cross the blood-brain barrier. Levodopa, the precursor of dopamine, crosses the blood brain barrier and relieves the symptoms of the disease. As levodopa is extensively metabolised in the periphery, only a small portion of a given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors. Carbidopa is a peripheral DDC inhibitor which reduces the peripheral metabolism of levodopa to dopamine, and thus, more levodopa is available to the brain. When decarboxylation of levodopa is reduced with the co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse reactions such as nausea is reduced.

With inhibition of the decarboxylase by a DDC inhibitor, catechol-*O*-methyltransferase (COMT) becomes the major peripheral metabolic pathway catalysing the conversion of levodopa to 3-Omethyldopa(3-OMD), a potentially harmful metabolite of levodopa. Entacapone is a reversible, specific and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa. Entacapone slows the clearance of levodopa from the bloodstream resulting in an increased area under the curve (AUC) in the pharmacokinetic profile of levodopa. Consequently the clinical response to each dose of levodopa is enhanced and prolonged.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Stacapolo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg and 200 mg/50 mg/200 mg film-coated tablets via a decentralized procedure according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. a generic application).

Vipharm S.A. has applied for marketing authorisations based on the documentation of Actavis.

The reference products were Stalevo® film-coated tablets in the same dosage combinations from Orion Corporation (Espoo, Finland).

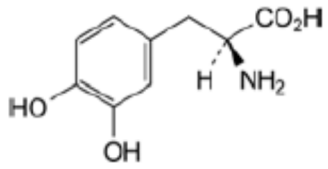
II.2 Drug substances

II.2.1 Levodopa

For the active substance levodopa a European Pharmacopoeia (Ph. Eur.) certificate of suitability (CEP) has been submitted.

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

Ph. Eur. name: levodopa
Chemical name: (2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid
Structure:



The active substance is white, crystalline powder, slightly soluble in water, practically insoluble in ethanol (96 per cent). It is freely soluble in 1 M hydrochloric acid and sparingly soluble in 0.1 M hydrochloric acid. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

Description of the manufacturing process, evidence of the structure, impurity profile of the active substance containing detailed information about genotoxic impurities, residual solvents and catalysts has been assessed during the CEP procedure.

The active substance is official in the Ph. Eur., additional specifications has been set for the active substance for residual solvent (as mentioned on the CEP) and particle size

distribution.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the 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 detail 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.

The retest period and the packaging material (double polyethylene bags /outer black/ placed in a polyethylene drum) have been mentioned on the CEP.

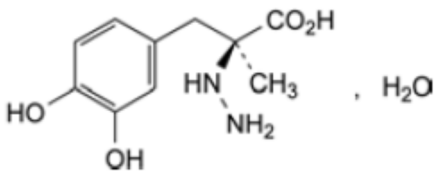
Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

II.2.2 Carbidopa

For the active substance carbidopa a CEP has been submitted.

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

Ph. Eur. name: carbidopa
Chemical name: (2S)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate
Structure:



The active substance is white or yellowish-white powder, slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids. Monohydrate crystal form is used for the drug product manufacture.

Description of the manufacturing process, evidence of the structure, impurity profile of the active substance containing detailed information about genotoxic impurities, residual solvents and catalysts have been assessed during the CEP procedure.

The active substance is official in the Ph. Eur., additional specifications has been set for the active substance for related substances by HPLC, residual solvent (as mentioned on the CEP) and particle size distribution.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the 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 detail 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.

The retest period and the packaging material (double polyethylene bags placed in a fibre drum) have been mentioned on the CEP.

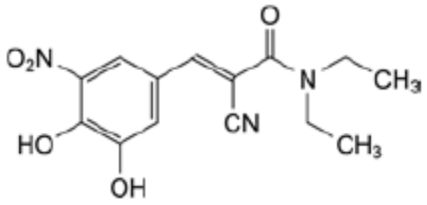
Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.2.3 Entacapone

For the active substance entacapone a CEP has been submitted.

Data on the quality and manufacture of the active substance was provided in the applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Ph. Eur. name: Entacapone
Chemical name: (2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide
Structure:



The active substance is greenish-yellow or yellow powder, practically insoluble in water, soluble or sparingly soluble in acetone, slightly soluble in anhydrous ethanol. It shows polymorphism. According to the CEP, the active substance manufacturer produces form-A.

Description of the manufacturing process, evidence of the structure, impurity profile of the active substance containing detailed information about genotoxic impurities, residual solvents and catalysts has been assessed during the CEP procedure.

The active substance is official in the Ph. Eur., additional specifications has been set for the active substance for residual solvents by GC (as mentioned on the CEP) and particle size distribution.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the 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 detail 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.

The retest period in the proposed packaging material (double polyethylene bag placed in a polyethylene container) is mentioned on the CEP.

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

II.3 Medicinal product

The aim of the pharmaceutical development was to formulate an immediate release compressed

oral dosage form with 4 different dosage combinations of levodopa/carbidopa/entacapone (LCE); 50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg, and 200/50/200 mg. The tablets were intended to show essential similarity with the reference products Stalevo® in the same dosage combination from Orion Corporation, Finland.

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 impurity profile the product is shown to be similar to the reference product.

Although based on the comparative dissolution profiles of the active substances the developed LDE products cannot be considered in-vitro equivalent (f_2) to the reference Stalevo tablets, the in vitro inequality does not affect the efficacy, quality and safety of the product, since the in-vivo bioequivalence studies prevail over the in vitro dissolution study,

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 have been formed:
- 50/12.5/200 mg film-coated tablets: oval, biconvex, film coated, brownish red tablets, 6.85 x 14.2 mm, marking “50” on one side and “LEC” on the opposite side;
- 100/25/200 mg film-coated tablets: oval, biconvex, film coated, brownish red tablets, 7.23 x 15.3 mm marking “100” on one side and “LEC” on the opposite side;
- 150/37.5/200 mg film-coated tablets: oval, biconvex, film coated, brownish red tablets, 7.68 x 16.2 mm, marking “150” on one side and “LEC” on the opposite side;
- 200/50/200 mg film-coated tablets: oval, biconvex, film coated, brownish red tablets, 8.21 x 17.2 mm, marking “200” on one side and “LEC” on the opposite side.

The excipients used in the finished products are:
- tablet core: croscarmellose sodium, hydroxypropylcellulose, trehalose dihydrate, cellulose, sodium sulfate, cellulose microcrystalline, magnesium stearate, 96 % ethanol (not present in final products) and purified water (not present in final products);
- the film coating is Opadry II red 85G35208, which contains a mixture of polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol 3350 (E1521), red iron dioxide (E172), lecithin (soya) (E322), yellow iron oxide (E172) and purified water.

All excipients, except Opadry II red 85G35208 film-coating agent and iron oxide comply with respective Ph. Eur. monograph. Red iron oxides comply with E172. Opadry II red 85G35208 is controlled according to an in-house specification. The ingredients of the coating mixture comply with Ph. Eur and Directive 2009/35/EC.

Compliance of the product with the general monograph of the Ph. Eur. on *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. 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 in HDPE containers sealed with an aluminium foil and closed with PP lids. Specifications and quality certificates for all packaging components are enclosed.

The conditions used in the stability studies were according to the ICH stability guideline.

Test results of bulk tablets comply with the release requirements if stored for 6 months in the prescribed packaging material.

The stability testing is performed according to a reduced stability testing protocol (matrixing) following the *Note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products* (CPMP/ICH/4101/00, February 2002), or the ICH Q1D. Based on the qualitative composition of the products, reduced testing by matrixing is acceptable.

Based on the results, a shelf-life of 2 years with no special storage conditions is approved.

The SmPC, the patient information 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 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 quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmaco-toxicological properties of levodopa, carbidopa and entacapone are well-known. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to levodopa, carbidopa and entacapone.

III.2 Pharmacology

Stacapolo is a fixed combination of levodopa, carbidopa, and entacapone. Of the three components, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone modify the peripheral metabolism of levodopa. All three active substances are well-known compounds. No further information was provided regarding the pharmacology of levodopa, carbidopa, and entacapone.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

No toxicity studies were submitted by the Applicant for the proposed fixed combination.

Published information on toxicological studies with levodopa, carbidopa, and entacapone was the basis for the evaluation.

Non-clinical data of levodopa, carbidopa and entacapone, tested alone or in combination, revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In repeated dose toxicity studies with entacapone, anemia most likely due to iron chelating properties of entacapone was observed. Regarding reproduction toxicity of entacapone, decreased foetal weight and a slightly delayed bone development were noticed in rabbits treated at systemic exposure levels in the therapeutic range. Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. The triple therapy is not recommended during pregnancy in humans.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Stacapolo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of levodopa, carbidopa and entacapone are well-known. As the combination is a generic product 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

Stacapolo is a fixed combination of levodopa, carbidopa, and entacapone. Of the three components, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone modify the peripheral metabolism of levodopa. Levodopa is a precursor of dopamine. The conversion of levodopa to dopamine in the brain is required for the therapeutic effect. Carbidopa is a selective, reversible and peripherally acting dopa decarboxylase (DDC) inhibitor that is routinely combined with levodopa. Entacapone is a reversible and peripherally acting catechol-O-methyltransferase (COMT) inhibitor. Both carbidopa and entacapone inhibit the metabolism of levodopa outside the central nervous system. The goal is to increase and prolong the availability of levodopa to the CNS from a single dose. Entacapone has been demonstrated to dose-dependently and reversibly inhibit COMT activity in red blood cells of healthy volunteers. Maximum inhibition (approximately 60%) was reached within 60 min with a single dose of 200 mg. The activity returned to baseline within 8 hours. Reversible inhibition was also observed following repeated dosing for 10 days. Entacapone has no antiparkinsonian effect per se. In the treatment of PD, entacapone is always administered with a levodopa/DDC inhibitor.

Therefore, a fixed combination was developed that contains entacapone as a reversible COMT inhibitor in addition to L-DOPA and carbidopa. This combination – levodopa/carbidopa/entacapone – is indicated for treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilized on levodopa/dopa decarboxylase (DDC) inhibitor treatment. The dose is individually titrated with a maximum recommended daily dose of 2,000 mg entacapone.

The application represents a generic submission.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption/distribution: There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone. Both levodopa and entacapone are rapidly absorbed and eliminated. Carbidopa is absorbed and eliminated slightly slower compared with levodopa. When given separately without the two other active substances, the bioavailability for levodopa is 15-33%, for carbidopa 40-70% and for entacapone 35% after a 200 mg oral dose. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone. The distribution volume of both levodopa (Vd 0.36-1.6 l/kg) and entacapone (Vdss 0.27 l/kg) is small while no data for carbidopa are available.

Levodopa is bound to plasma protein only to a minor extent of about 10-30% and carbidopa is bound approximately 36%, while entacapone is extensively bound to plasma

proteins (about 98%) –mainly to serum albumin. At therapeutic concentrations, entacapone does not displace other extensively bound active substances (e.g. warfarin, salicylic acid, phenylbutazone, or diazepam), nor is it displaced to any significant extent by any of these substances at therapeutic or higher concentrations.

Biotransformation and elimination: Levodopa is extensively metabolized to various metabolites: decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT) being the most important pathways. Carbidopa is metabolized to two main metabolites which are excreted in the urine as glucuronides and unconjugated compounds. Unchanged carbidopa accounts for 30% of the total urinary excretion. Entacapone is almost completely metabolized prior to excretion via urine (10 to 20%) and bile/faeces (80 to 90%). The main metabolic pathway is glucuronidation of entacapone and its active metabolite, the cis-isomer, which accounts for about 5% of plasma total amount.

Total clearance for levodopa is in the range of 0.55-1.38 l/kg/h and for entacapone is in the range of 0.70 l/kg/h. The elimination-half life is (t1/2) is 0.6-1.3 hours for levodopa, 2-3 hours for carbidopa and 0.4-0.7 hours for entacapone, each given separately. Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs on repeated administration.

Data from *in vitro* studies using human liver microsomal preparations indicate that entacapone inhibits cytochrome P450 2C9 (IC50 ~ 4 μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19.

IV.2.2 Bioequivalence studies

Bioequivalence of the applied products was evaluated in two pivotal single-dose, two-way crossover partial replicated studies under fasting conditions.

These studies were carried out with the 50 mg/12.5 mg/200 mg and with 200 mg/50 mg/200 mg strengths.

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

Biowaiver

The applicant seeks biowaiver for the other two strengths. The applicant states that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) concerning biowaivers were met.

According to the current guidelines a bracketing approach is allowed in order to claim the bioequivalence of the intermediate dosage forms.

The two formulations fulfil this requirement when bioequivalence is justified for the highest and the lowest strength. Furthermore, the amount of the active ingredients as a percentage of the tablet weight, represent the extremes in the highest and the lowest strengths. Therefore, bioequivalence of the intermediate dosage forms can be claimed.

Similarities of in-vitro dissolution profiles were also justified.

Study with the 50 mg/12.5 mg/200 mg strength

The main objective of this study was to assess the bioequivalence of the fixed dose combination tablet containing levodopa/carbidopa/entacapone 50 mg/12.5 mg/ 200 mg of Actavis PTC ehf, Iceland (Test, T) and Stalevo® tablet of Orion Corporation, Finland of the same strength (Reference, R), in healthy adult subjects of either sex, under fasting condition.

The design of this investigation was a randomized, open label, cross over, three-period, three sequence, single dose, partial replicate, reference-scaled, average bioequivalence study (BE) study with an adequate washout period between 2 subsequent periods, in healthy male subjects under fasting conditions.

The analytical methods comprise LC-MS/MS technique; solid phase extraction method for levodopa and carbidopa while liquid phase extraction method for entacapone.

The choice of sample size was enough to prove the bioequivalence between the test and reference products with a power of at least 80% and at $\alpha = 5\%$. (In the determination of sample size 30% intra-subject CV and a true ratio of the test and reference product of 90-105% was assumed.)

The pharmacokinetic parameters were:

- primary: AUC_{0-t}, C_{max},
- secondary/other : $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, T_{max}, K_{el}, $t_{1/2}$

The statistical methods used in evaluation were:

- descriptive statistics: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric mean (GM) for test (T) and reference (R1 and R2) PK data;
- log-transformation of $AUC_{0-\infty}$, AUC_{0-t} and C_{max} data;
- evaluation using a linear mixed-effects model (PROC MIXED, SAS®), with the main effects of treatment, period and sequence as fixed effects and subjects nested within sequence as random effect in ANOVA;
- calculation of 90% confidence intervals for the difference between the least square means (LSM) for the parameters AUC_{0-t}, $AUC_{0-\infty}$, C_{max} consistence with the two-sided tests for bioequivalence;
- non-parametric analysis of T_{max} on untransformed data, using Wilcoxon signed rank test.

The next table summarises the results of this study.

Pharmacoki-netic parameter	Ratio (T/R)	90% Confidence interval
Levodopa		
AUC_{0-t}	104.54	101.30 – 107.87
C_{max}	101.87	97.14 – 106.82
Carbidopa		
AUC_{0-t}	108.15	100.74 – 116.11
C_{max}	110.91	102.68 – 119.80
Entacapone		
AUC_{0-t}	103.76	100.14 – 107.52
C_{max}	100.35	90.64 – 111.09

Results derived from the analysis of log-transformed primary efficacy parameters C_{max} and AUC_{0-t} of levodopa, carbidopa and entacapone, the T/R ratios were included within the acceptance interval of 80% - 125%, and their 90% confidence intervals in the pre-defined acceptance range depending on intra-subject variability calculated from study data. Thus, results support the bioequivalence between the test and reference products.

Based on the clinical laboratory assessments, both study medications were found to be safe and well tolerated.

Study with the 200 mg/50 mg/200 mg strength

The main objective of this study was to assess the bioequivalence of fixed dose combination tablet containing levodopa/carbidopa/entacapone 200 mg/50 mg/200 mg of Actavis PTC ehf, Iceland and Stalevo® tablet of Orion Corporation, Finland of the same strength, in healthy adult subjects of either sex, under fasting condition.

The design of this investigation was a randomized, open label, cross over, three-period, three sequence, single dose, partial replicate, reference-scaled, average bioequivalence study (BE) study with an adequate washout period between 2 subsequent periods, in healthy male subjects under fasting conditions.

The analytical methods were the same as in the previous study.

The choice of sample size was enough to prove the bioequivalence between the test and reference products with a power of at least 80% and at $\alpha = 5\%$ significance level. (In the sample size estimation 30% intra-subject CV and a true ratio of the test and reference product of 90-105% was assumed.)

The pharmacokinetic parameters were as follows:

- primary: AUC_{0-t}, C_{max},
- secondary/other : $AUC_{0-\infty}$, AUC_{0-t} /$AUC_{0-\infty}$, T_{max}, K_{el} , $t_{1/2}$.

The statistical methods used in evaluation were as follows:

- descriptive statistics: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric mean (GM) for test (T) and reference (R1 and R2) PK data,
- log-transformation of AUC0-∞, AUC0-t and Cmax data,
- evaluation using a linear mixed-effects model (PROC MIXED, SAS®), with the main effects of treatment, period and sequence as fixed effects and subjects nested within sequence as random effect in ANOVA,
- calculation of 90% confidence intervals for the difference between the least square means (LSM) for the parameters AUC0-t, AUC0-∞, Cmax consistence with the two-sided tests for bioequivalence,
- non-parametric analysis of Tmax on untransformed data, using Wilcoxon signed rank test.

The next table summarises the results of this study.

Pharmacoki-netic parameter	Ratio (T/R)	90% Confidence interval
Levodopa		
AUC_{0-t}	95.63	91.56 – 99.88
C_{max}	92.40	88.02 – 97.00
Carbidopa		
AUC_{0-t}	100.51	90.37 – 111.78
C_{max}	97.19	89.17 – 105.93
Entacapone		
AUC_{0-t}	95.40	91.94 – 99.00
C_{max}	90.68	79.37 – 103.59

For all PK parameters listed in the current bioequivalence guideline, the 90% confidence interval (CI) was within the 80.00-125.00% range for carbidopa and levodopa.

For entacapone the AUC 90% CI was within the 80.00-125.00% range, but the C_{max} 90% CI not (79.37). However, it is clear that intra-individual CV for C_{max} > 30% (37.20) and therefore, according to the predefined rules, the 90% CI (needed to fit) is within the 76.06 – 131.47 % range.

Results derived from the analysis of log-transformed primary efficacy for primary efficacy parameters C_{max} and AUC_{0-t} of levodopa, carbidopa and entacapone, the T/R ratios were included within the acceptance interval of 80% - 125%, and their 90% confidence intervals in the pre-defined acceptance range depending on intra-subject variability calculated from study data. Thus, results support the bioequivalence between the test and reference products.

Based on the clinical laboratory assessments both study medications were found to be safe and well tolerated.

Conclusion on bioequivalence studies

The studies proved the bioequivalence of the lowest and highest strengths of the test and reference products.

Results of the two bioequivalence studies can be extrapolated to strengths 100 mg/25 mg/ 200 mg and 150 mg/37.5 mg/200 mg strengths according to conditions in the *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Based on the submitted bioequivalence studies the levodopa/carbidopa/entacapone film-coated tablets of Actavis are considered bioequivalent with Stalevo® tablets of Orion Corporation. The present application for Stacapolo tablets utilized the documentation of the Actavis preparations.

IV.3 Pharmacodynamics

Clinical pharmacological studies to evaluate the pharmacodynamics of Stacapolo film-coated tablets were not performed.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of levodopa, carbidopa, and entacapone.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance system

The applicant, i.e. the future marketing authorisation holder has submitted a signed Summary of the Pharmacovigilance system. The Pharmacovigilance System Master File complies with the new legal requirements as set out in the Commission implementing regulation and as detailed in the Good Vigilance Practice module. The RMS considers the Summary acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• impulse control disorders (compulsive buying and spending, compulsive or binge eating), • rhabdomyolysis, • neuroleptic malignant syndrome, • liver and biliary system disorder and liver laboratory abnormalities, • depression with suicidal tendencies, • gastrointestinal haemorrhage, • colitis, • thrombocytopenia, • orthostatic hypotension, • myocardial infarction and other ischaemic heart disease.
Important potential risks	• severe skin and severe allergic reactions, • prostate cancer • medication error
Missing information	pregnancy

Table of on-going and Planned Additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

No additional pharmacovigilance activities are on-going and none are planned.

Summary of Post Authorization Efficacy Development Plan

No post-authorisation efficacy studies are planned.

Summary Table of Risk Minimization Measures

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Impulse control disorders (compulsive buying and spending, compulsive or binge eating)	Warning in section 4.4 of SmPC to development of impulse control disorders, i.e. pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating. Listed in SmPC section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Rhabdomyolysis	In section 4.3 of SmPC - Contraindications - a previous history of rhabdomyolysis is mentioned. Warning in section 4.4 of SmPC to "rhabdomyolysis". Listed in SmPC section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Neuroleptic malignant syndrome	In section 4.3 of SmPC - Contraindications - a previous history of neuroleptic malignant syndrome (NMS) is mentioned. Warning in section 4.4 of SmPC to "NMS". Listed in SmPC section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Liver and biliary system disorder and liver laboratory abnormalities	Severe hepatic impairment is contraindication for Stacapolo. Periodic evaluation of hepatic function is recommended during extended therapy with Stacapolo. Hepatitis with mainly cholestatic features and Hepatic function test abnormal are listed in section 4.8 of SmPC as adverse reactions. Other routine risk minimisation measures: prescription-only medicine.	None.
Depression with suicidal tendencies	Warning in section 4.4 of SmPC to depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current psychosis should be treated with caution. Listed in section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Gastrointestinal haemorrhage	Serious events of gastrointestinal heamorrhage have been identified from the clinical trials with combination of levodopa, carbidopa and entacapone or entacapone combined with levodopa/DDC inhibitor. Listed in section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Colitis	Warning in section 4.4 of SmPC to prolonged or persistent diarrhoea appearing during use of entacapone, which may be a sign of colitis. Listed in section 4.8 of SmPC. Other routine risk minimisation measures: prescription-only medicine.	None.

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Thrombocytopenia	Adequate information is included in SmPC section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Orthostatic hypotension	Warning in section 4.4 of SmPC to orthostatic hypotension. Listed in section 4.8. Other routine risk minimisation measures: prescription-only medicine.	None.
Myocardial infarction and other ischaemic heart disease	Warning in section 4.4 of SmPC to Stacapolo therapy administered cautiously to patients with ischemic heart disease. In Section 4.8. Ischaemic heart disease events other than myocardial infarction (e.g. angina pectoris), irregular heart rhythm and myocardial infarction are presented as adverse effects. Other routine risk minimisation measures: prescription-only medicine.	None.
Severe skin and severe allergic reactions	In the section 4.3 Contraindications. Hypersensitivity to the active substances or to any of the excipients" is mentioned. In section 4.8 Undesirable effects. Rash, angioedema and urticarial are mentioned as adverse reactions. Other routine risk minimisation measures: prescription-only medicine.	None.
Prostate cancer	Other routine risk minimisation measures: prescription-only medicine.	None.
Medication error	The SmPC and the patient leaflet should be read carefully because they contain important information on the correct use of the product in order to: - prevent "wrong medication" error, - prevent "wrong dose" (strength, form, amount) medication error, - prevent "wrong- route administration" medication error, - prevent "wrong patient" medication error. Other routine risk minimisation measures: prescription-only medicine.	None.
Pregnancy	Adequate information is included in SmPC section 4.6 and in the patient leaflet. Stacapolo should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus. Women should not breast-feed during treatment with Stacapolo. Other routine risk minimisation measures: prescription-only medicine.	None.

IV.6.3 Periodic Safety Update Reports

With regard to PSUR submission, the marketing authorization holder should take the following into account.

Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check this web-portal for the data lock point and frequency of submission of the next PSUR.

According to the EURD list and frequency of submission of periodic safety updated reports published on 1 December 2014 the PSUR cycle is 3 years for the combination of levodopa/carbidopa/entacapone. The next data lock point is 17. 10. 2015 and PSURs are required for products referred to Article 10(1).

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

This application concerns a generic fixed combination of levodopa, carbidopa, and entacapone. The indication is treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

To support the application the applicant has adequately demonstrated bioequivalence between Stacapolo film-coated tablets and the reference product Stalevo 50 mg/12.5 mg/200 mg and 200 mg/50 mg/200mg film-coated tablets.

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present generic applications concern four strengths of fix combinations containing levodopa/carbidopa/entacapone active substances. The holder of the marketing authorisation is Vipharm S.A., Finland.

The products are indicated for the treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment.

The application has been based on the Article 10(1) of Directive 2001/83/EC and therefore no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product and reference products in two studies.

The reference (originator) products were Stalevo 50mg/12.5mg/200mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 and 200 mg/50 mg/200 mg film-coated tablets by Orion Corporation, approved for more than 10 years in the European Economic Area.

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.

The RMS found the products approvable. The recommended classification has been prescription-only medicine.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Stacapolo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg and 200 mg/50 mg/200 mg film-coated tablets.

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