Public Assessment Report

Decentralised Procedure

Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg Film-coated tablets
Levodopa/Carbidopa/Entacapone Accord 150 mg/37.5 mg/200 mg Film-coated tablets
Levodopa/Carbidopa/Entacapone Accord 125 mg/31.25 mg/200 mg Film-coated tablets
Levodopa/Carbidopa/Entacapone Accord 200 mg/50 mg/200 mg Film-coated tablets
Levodopa/Carbidopa/Entacapone Accord 50 mg/12.5 mg/200 mg Film-coated tablets
Levodopa/Carbidopa/Entacapone Accord 75 mg/18.75 mg/200 mg Film-coated tablets

(Levodopa, carbidopa and entacapone)

Procedure No: UK/H/5908/001-006/DC

UK Licence No: PL 20075/0417-0422

Accord Healthcare Limited
LAY SUMMARY

Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg Film-coated tablets

(levodopa, carbidopa and entacapone)

The products Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets may be referred to as ‘Levodopa/Carbidopa/Entacapone Accord film-coated tablets’ this report.

This is a summary of the Public Assessment Report (PAR) for Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (PL 20075/0417-0422; UK/H/5908/001-006/DC). It explains how Levodopa/Carbidopa/Entacapone Accord film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Levodopa/Carbidopa/Entacapone Accord film-coated tablets.

For practical information about using Levodopa/Carbidopa/Entacapone Accord film-coated tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Levodopa/Carbidopa/Entacapone Accord film-coated tablets and what are they used for?
Levodopa/Carbidopa/Entacapone Accord film-coated tablets are ‘generic’ medicines. This means that Levodopa/Carbidopa/Entacapone Accord film-coated tablets are similar to reference medicines already authorised in the European Union (EU) called Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (Orion Corporation, Finland).

Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets may be referred to as ‘Stalevo film-coated tablets’ in this report.

Levodopa/Carbidopa/Entacapone Accord film-coated tablets are used for the treatment of Parkinson’s disease.

How do Levodopa/Carbidopa/Entacapone Accord film-coated tablets work?
Parkinson’s disease is caused by low levels of a substance called dopamine in the brain.

Levodopa/Carbidopa/Entacapone Accord film-coated tablets contain three active substances (levodopa, carbidopa and entacapone) in each film-coated tablet. Levodopa increases the amount of dopamine and hence reduces the symptoms of Parkinson’s disease. Carbidopa and entacapone improve the antiparkinson effects of levodopa.
How are Levodopa/Carbidopa/Entacapone Accord film-coated tablets used?
Levodopa/Carbidopa/Entacapone Accord film-coated tablets are taken by mouth.

Levodopa/Carbidopa/Entacapone Accord film-coated tablets can only be obtained with a prescription. The tablets should be taken exactly as told by the doctor or pharmacist. The patient should check with the doctor or pharmacist if not sure.

For adults and elderly:
The patient’s doctor will tell the patient exactly how many tablets of this medicine 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 responds to treatment, the patient’s doctor may suggest a higher or lower dose.

If the patient is taking Levodopa/Carbidopa/Entacapone Accord 50 mg/12.5 mg/200 mg, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg or 150 mg/37.5 mg/200 mg tablets, no more than 10 tablets per day should be taken.

If the patient is taking Levodopa/Carbidopa/Entacapone Accord 200 mg/50 mg/200 mg, he/she should not take more than 7 tablets of this strength per day.

The patient should speak to the doctor or pharmacist if he/she thinks the effect of this medicine is too strong or too weak, or if he/she experiences possible side effects.

For further information on how Levodopa/Carbidopa/Entacapone Accord film-coated tablets are used, please refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Levodopa/Carbidopa/Entacapone Accord film-coated tablets have been shown in studies?
As Levodopa/Carbidopa/Entacapone film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets are bioequivalent to the reference medicines, Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets, respectively. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (Accord Healthcare Limited) provided data from the published literature on levodopa, carbidopa and entacapone.

What are the possible side effects of Levodopa/Carbidopa/Entacapone Accord film-coated tablets?
Because Levodopa/Carbidopa/Entacapone Accord film-coated tablets are generic medicines and are bioequivalent to the reference medicines Stalevo film-coated tablets (Orion Corporation, Finland), the possible side effects are taken as being the same as those of the reference medicines.

For the full list of restrictions, see the package leaflet available on the MHRA website.
Why are Levodopa/Carbidopa/Entacapone Accord film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Levodopa/Carbidopa/Entacapone Accord film-coated tablets have been shown to have comparable quality and to be bioequivalent to Stalevo film-coated tablets (Orion Corporation, Finland). Therefore, the view was that, as for Stalevo film-coated tablets (Orion Corporation, Finland), the benefits outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Levodopa/Carbidopa/Entacapone Accord film-coated tablets?
A Risk Management Plan has been developed to ensure that Levodopa/Carbidopa/Entacapone Accord film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Levodopa/Carbidopa/Entacapone Accord film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Levodopa/Carbidopa/Entacapone Accord film-coated tablets
Austria (PL 20075/0417-8; UK/H/5908/001-002/DC and PL 20075/0421; UK/H/5908/005/DC only), Cyprus, Denmark, Finland, France, Italy, Malta, The Netherlands, Sweden and the UK agreed to grant Marketing Authorisations for Levodopa/Carbidopa/Entacapone Accord film-coated tablets on 04 December 2015. Marketing Authorisations were granted in the UK to Accord Healthcare Limited on 23 December 2015.

The full PAR for Levodopa/Carbidopa/Entacapone Accord film-coated tablets follows this summary.

For more information about treatment with Levodopa/Carbidopa/Entacapone Accord film-coated tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2016.
SCIENTIFIC DISCUSSION

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Scientific discussion

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (PL 20075/0417-0422; UK/H/5908/001-006/DC) could be approved. These are prescription-only medicines (POM) 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 products may be referred to as Levodopa/Carbidopa/Entacapone Accord film-coated tablets in this report.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria (Procedures UK/H/5908/001-002/DC and UK/H/5908/005/DC only), only), Cyprus, Denmark, Finland, France, Italy, Malta, The Netherlands and Sweden as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator medicinal products Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (Orion Corporation, Finland) which were authorised in the EEA via the Centralised Procedure.

Stalevo 50 mg/12.5 mg/200 mg, 100 mg/25 mg/200 mg, 150mg/37.5 mg /200 mg and 200 mg/50 mg/200 mg film-coated tablets were authorised on 17 October 2003. Stalevo 75 mg/18.75 mg/200 mg and 125 mg/31.25 mg/200 mg film-coated tablets were authorised on 27 March 2009, as extension applications for new dosage strengths to the existing Marketing Authorisations for Stalevo film-coated tablets authorised on 17 October 2003.

The active ingredients in these products are levodopa, carbidopa and entacapone. Levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone inhibit the peripheral metabolism of levodopa.

Levodopa is a precursor of dopamine and is given as replacement therapy in Parkinson's disease.

Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of side effects.

Entacapone is a reversible, specific and mainly peripherally acting catechol-O-methyltransferase (COMT) inhibitor. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) mainly in peripheral tissues. The amount of levodopa available to the brain is increased, thus prolongs the clinical response to levodopa.

Three bioequivalence studies were submitted to support these applications; two bioequivalence studies comparing the applicant’s test Fixed Drug Formulation (FDC) of Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg tablet with the reference product Stalevo tablets containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg (Orion Pharma GmbH, Germany), under fasting conditions and one bioequivalence study comparing the applicant’s test product FDC of Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg tablet versus the reference product Stalevo tablets containing Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg (Orion Corporation, Finland).
under fasting conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The Member States considered that the applications could be approved at the end of procedure (Day 210) on 04 December 2015. After a subsequent national phase, licences were granted in the UK to Accord Healthcare Limited on 23 December 2015.

II QUALITY ASPECTS

II.1 INTRODUCTION
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Description and composition

1. Levodopa/Carbidopa/Entacapone 100 mg/25 mg/200 mg strength tablets are light brown to greyish-red coloured, oval-shaped approximately 16.7 mm in width, film-coated with debossed with ‘100’ on one side, and plain on the other.

   Each Levodopa/Carbidopa/Entacapone 100 mg/25 mg/200 mg tablet contains 100 mg of levodopa, 25 mg of carbidopa and 200 mg of entacapone.

2. Levodopa/Carbidopa/Entacapone 150 mg/37.5 mg/200 mg strength tablets are light brown to grayish red coloured, elongated-ellipse shaped, approximately 16.2 mm in length and 10.2 mm in width and film-coated with debossed “150” on one side and plain on other side.

   Each Levodopa/Carbidopa/Entacapone 150 mg/37.5 mg/200 mg tablet contains 150 mg of levodopa, 37.5 mg of carbidopa and 200 mg of entacapone.

3. Levodopa/Carbidopa/Entacapone 125 mg/31.25 mg/200 mg strength tablets are light brown to light pink coloured, elongated-ellipse shaped, approximately 15.2 mm in length and 9.7 mm in width and film-coated with debossed “125” on one side and plain on other side.

   Each Levodopa/Carbidopa/Entacapone 125 mg/31.25 mg/200 mg tablet contains 125 mg of levodopa, 31.25 mg of carbidopa and 200 mg of entacapone.
4. Levodopa/Carbidopa/Entacapone 200 mg/50 mg/200 mg strength tablets are dark brownish red
coloured, oval shaped, approximately 19.15 mm in length and 9.05 mm in width and film-coated
with debossed "200" on one side and plain on other side.

Each Levodopa/Carbidopa/Entacapone 200 mg/50 mg/200 mg tablet contains 200 mg of
levodopa, 50 mg of carbidopa and 200 mg of entacapone.

5. Levodopa/Carbidopa/Entacapone 50 mg/12.5 mg/200 mg strength tablets are light brown to
grayish red coloured, round, approximately 11.3 mm in diameter, biconvex and film-coated with
debossed “50” on one side and plain on other side.

Each Levodopa/Carbidopa/Entacapone 50 mg/12.5 mg/200 mg tablet contains 50 mg of
levodopa, 12.5 mg of carbidopa and 200 mg of entacapone.

6. Levodopa/Carbidopa/Entacapone 75 mg/18.75 mg/200 mg strength tablets are light brown to
light pink coloured, oval shaped, approximately 15.2 mm in length and 7.2 mm in width and
film-coated with debossed “75” on one side and plain on other side.

Each Levodopa/Carbidopa/Entacapone 75 mg/18.75 mg/200 mg contains 75 mg of levodopa,
18.75 mg of carbidopa and 200 mg of entacapone.

The products also contain pharmaceutical excipients in the tablet cores and coatings, namely
microcrystalline cellulose, crospovidone (Type B), Povidone K-30, magnesium stearate, sodium citrate,
hypromellose, macrogol 6000, titanium dioxide (E171), polysorbate 80 and red iron oxide (E172).

In addition, Levodopa/Carbidopa/Entacapone Accord 50 mg/12.5 mg/200 mg, 100 mg/25 mg /200 mg
and 150 mg/37.5 mg/200 mg film-coated tablets contain yellow iron oxide (E172). Appropriate
justification for the inclusion of each excipient has been provided.

With the exception of red iron oxide (E172) and yellow iron oxide (E172), all excipients comply with
their respective European Pharmacopoeia monographs. Red iron oxide (E172) and yellow iron oxide
(E172) are in compliance with the current EU Directive concerning the use of colouring agents.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

The products are packaged in high-density polyethylene (HDPE) bottles, with child-resistant
polypropylene closures. Each HDPE bottle contains 1 silica gel canister closures.

The products are available in pack sizes of 30, 100 and 130 tablets film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging
components. All primary packaging complies with current European regulations concerning materials in
contact with foodstuff.
II.2 DRUG SUBSTANCE

LEVDOPA

INN: Levodopa
Chemical name: (2S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid
Molecular formula: C₉H₁₁NO₄
Structure:

Mr: 197.2
Appearance: White or almost white, crystalline powder.
Solubility: 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.

Levodopa is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, levodopa, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

DRUG SUBSTANCE - CARBIDOPA

INN: Carbidopa
Chemical name: (2S)-3-(3,4-Dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate
Molecular formula: C₁₀H₁₄N₂O₄.H₂O
Structure:

Mr: 244.2
Appearance: White or yellowish-white powder.
Solubility: 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.

Carbidopa is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, carbidopa, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

DRUG SUBSTANCE - ENTACAPONE

INN: Entacapone
Chemical name: (2E)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide
Molecular formula: C₁₄H₁₅N₃O₅
Structure:

\[
\text{\begin{tikzpicture}
\begin{scope}
\path (0,0) coordinate (O);
\path (1,0) coordinate (A);
\path (2,0) coordinate (B);
\path (3,0) coordinate (C);
\path (4,0) coordinate (D);
\path (0,1) coordinate (E);
\path (1,1) coordinate (F);
\path (2,1) coordinate (G);
\path (3,1) coordinate (H);
\path (4,1) coordinate (I);
\draw (O) -- (A) -- (B) -- (C) -- (D);
\draw (A) -- (E) -- (I); 
\draw (B) -- (F); 
\draw (C) -- (G); 
\draw (D) -- (H); 
\end{scope}
\end{tikzpicture}}
\]

Mr: 305.3
Appearance: A greenish yellow or yellow powder.
Solubility: Practically insoluble in water, soluble or sparingly soluble in acetone, and slightly soluble in anhydrous ethanol.

Entacapone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, entacapone, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable film-coated tablets containing levodopa, carbidopa and entacapone, which were bioequivalent to Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (Orion Corporation, Finland).

Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products and the respective reference products Stalevo 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets (Orion Pharma, Finland). The dissolution and impurity profiles were satisfactory.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Based on production-scale/near to production-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future production-scale batches.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, the following shelf-lives have been accepted:
- 3 years for product packaged in in unopened HDPE bottles.
- 6 months after first opening, for product in opened HDPE bottles.

There are no special temperature storage conditions required for the products.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Levodopa/Carbidopa/Entacapone Accord film-coated tablets, from a quality point of view.

II.5 Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labels
The SmPCs, PILs and labelling text are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website.

The current labelling is presented below:
Levodopa/Carbidopa/Entacapone Accord film-coated tablets:

Each film-coated tablet contains 100 mg of levodopa, 25 mg of carbidopa and 200 mg of entacapone.

Read the package leaflet before use. Oral use.

Keep out of the sight and reach of children. Should be used within 6 months after first opening.

Size: 50 x 50 x 86 mm
Levodopa/Carbidopa/Entacapone Accord 150 mg/37.5 mg/200 mg film-coated tablets:

- **Active Substances:** Levodopa 150 mg, Carbidopa 37.5 mg, Entacapone 200 mg.
- **Uses:** Treatment of Parkinson’s disease.
- **Dosage:** Oral use.
- **Storage:** Keep out of the sight and reach of children.
- **Expiration:** Should be used within 6 months after first opening.

Size: 50 x 50 x 86 mm
Levodopa/Carbidopa/Entacapone Accord 125 mg/31.25 mg/200 mg film-coated tablets:

Size: 50 x 50 x 86 mm
Levodopa/Carbidopa/Entacapone Accord 200 mg/50 mg/200 mg film-coated tablets:

Size: 50 x 50 x 86 mm
Levodopa/Carbidopa/Entacapone Accord 50 mg/12.5 mg/200 mg film-coated tablets:

- Each film-coated tablet contains 50 mg of levodopa, 12.5 mg of carbidopa, and 200 mg of entacapone.
- Oral use.
- Keep out of the sight and reach of children.
- Should be used within 6 months after first opening.

Read the package leaflet before use.

Size: 48 x 48 x 70 mm
Levodopa/Carbidopa/Entacapone Accord film-coated tablets

Each film-coated tablet contains 75 mg of levodopa, 18.75 mg of carbidopa and 200 mg of entacapone.

Read the package leaflet before use. Oral use.

Keep out of the sight and reach of children.

Should be used within 6 months after first opening.

PLMA Holder: Accord Healthcare Limited
Sage House, 319 Priner road, North Harrow
Middlesex, HA1 4HF, United Kingdom

100 film-coated tablets

Size: 50 x 50 x 0.7 mm

110 mm

40 mm
III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of levodopa, carbidopa and entacapone are well-known, no new non-clinical data are required and none have been provided.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the applications are for generic versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been licensed for over 10 years.

It is recommended that Marketing Authorisations are granted for Levodopa/Carbidopa/Entacapone Accord film-coated tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics
The clinical pharmacology of levodopa, carbidopa and entacapone is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacokinetic data is provided or required for these applications.

The Marketing Authorisation Holder submitted the following bioequivalence studies to support the applications:

Study 1
An open-label, randomised, single-dose, three-period, two-treatment, three-sequence, partial replicated, crossover, bioequivalence study comparing the test product Fixed Drug Formulation (FDC) of Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg tablet (Torrent Pharmaceuticals Limited) versus the reference product Stalevo tablets (containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg; Orion Corporation, Finland) in healthy human volunteers under fasting conditions.
Subjects were administered a single dose of either the test or reference product with 200 ml of water at room temperature after at least an 8-hour overnight fast, according to the randomisation schedule. Blood sampling was performed pre-dose and up to 18 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below:

**Intra-subject CV (ISCV) of Reference formulation for C\text{\text{max}}, Method of Bioequivalence analysis and Bioequivalence acceptance range**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>% ISCV</th>
<th>Method for Bioequivalence Analysis</th>
<th>Bioequivalence Acceptance Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>22.99</td>
<td>Two one-sided tests Procedure</td>
<td>80.00-125.00%</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>27.04</td>
<td>Two one-sided tests Procedure</td>
<td>80.00-125.00%</td>
</tr>
<tr>
<td>Entacapone</td>
<td>47.88</td>
<td>Scaled-average-bioequivalence procedure</td>
<td>70.80-141.24%</td>
</tr>
</tbody>
</table>

**Evaluation of bioequivalence**

**Pharmacokinetic parameters (geometric Least Square Mean [LSM] ratios and confidence intervals [CI]) for levodopa, carbidopa and entacapone.**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Geometric LSM Ratio (%)</th>
<th>(Lower limit - Upper limit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entacapone:</td>
<td>Ln(C\text{max})</td>
<td>96.36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Geometric LSM Ratio (%)</th>
<th>90% CI (Lower limit - Upper limit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa:</td>
<td>Ln(C\text{max})</td>
<td>104.98</td>
</tr>
<tr>
<td></td>
<td>Ln(AUC(0-t))</td>
<td>94.40</td>
</tr>
<tr>
<td>Carbidopa:</td>
<td>Ln(C\text{max})</td>
<td>82.01</td>
</tr>
<tr>
<td></td>
<td>Ln(AUC(0-t))</td>
<td>81.78</td>
</tr>
<tr>
<td>Entacapone:</td>
<td>Ln(AUC(0-t))</td>
<td>100.25</td>
</tr>
</tbody>
</table>

\(AUC_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours

\(C_{\text{max}}\) maximum plasma concentration

**Bioequivalence Discussion and Conclusion**

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for \(C_{\text{max}}\) and AUC values.

The intra-subject coefficient of variance (%ISCV) of the reference formulation for the \(C_{\text{max}}\) of levodopa and carbidopa was < 30%; hence two one sided tests procedure was used for the bioequivalence claim for these analytes, with confidence limits of 80.00% to 125.00% set as criteria for bioequivalence. The intra-subject coefficient of variance (%ISCV) of the reference formulation for \(C_{\text{max}}\) of entacapone was > 30%, hence the scaled average procedure was used for the bioequivalence claim for this analyte, with widen confidence limits of 70.84% to 141.24% set as criteria for bioequivalence.

The results indicate that the bioequivalence criteria are met for levodopa and entacapone as the
AUC(0-t) and C_max values for these analytes lie within acceptance limits. However the AUC(0-t) and C_max values for carbidopa lie outside the acceptance limits and do not support the bioequivalence criteria. Hence, the data from this study do not support the claim that the applicant’s test product is bioequivalent to the reference product under fasting conditions.

As Study 1 did not demonstrate bioequivalence for carbidopa, the applicant also submitted the following studies:

**Study 2**

An open-label, randomised, four-period, two-treatment, two-sequence, replicate, crossover, single-dose bioequivalence study comparing the test product FDC of Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg tablet (Torrent Pharmaceuticals Limited) versus the reference product Stalevo tablets containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg (Orion Corporation, Finland) in healthy human volunteers under fasting conditions.

Subjects were administered a single dose of either the test or reference product with 200 ml of water at room temperature after at least an 8-hour overnight fast, according to the randomisation schedule. Blood sampling was performed pre-dose and up to 12 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below:

**Evaluation of Bioequivalence**

| Pharmacokinetic parameters (geometric Least Square Mean [LSM] ratios and confidence intervals [CI]) for levodopa, carbidopa and entacapone. |
|---|---|---|
| **PK Parameters** | **Geometric LSM Ratio (%)** | **90% CI (Lower limit-Upper limit)** |
| Entacapone: | | |
| Ln(Cmax) | 99.44 | 88.94 – 111.18 |
| Two One-sided Tests Procedure: | | |
| PK Parameters | **Geometric LSM Ratio (%)** | (Lower limit-Upper limit) |
| Levodopa: | | |
| Ln(Cmax) | 99.72 | 95.68 – 103.92 |
| Ln(AUC(0-t)) | 95.80 | 92.66 – 99.04 |
| Carbidopa: | | |
| Ln(Cmax) | 90.81 | 83.94 – 98.25 |
| Ln(AUC(0-t)) | 93.30 | 87.05 – 100.01 |
| Entacapone: | | |
| Ln(AUC(0-t)) | 95.67 | 92.00 – 99.48 |

AUC_{(0-t)} area under the plasma concentration-time curve from time zero to t hours  
C_{max} maximum plasma concentration

**Bioequivalence Discussion and Conclusion**

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for C_{max} and AUC values.

The intra-subject coefficient of variance (%ISCV) of the reference formulation for C_{max} of levodopa and carbidopa were < 30%; hence the two one-sided tests procedure was used for the bioequivalence claim for these analytes, with confidence limits of 80.00% to 125.00% set as criteria for bioequivalence. The intra-subject coefficient of variance (%ISCV) of the reference formulation for C_{max} of
entacapone was > 30%, hence the scaled average procedure was used for the bioequivalence claim for this analyte, with widen confidence limits of 73.61% to 135.84% set as criteria for bioequivalence.

The results indicate that the bioequivalence criteria were met for levodopa, carbidopa and entacapone as the $\text{AUC}_{0-t}$ and $C_{\text{max}}$ values for these analytes lie within acceptance limits. Hence the data from this study support the claim that the applicant’s test product Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg tablet is bioequivalent to the reference product Stalevo tablets (containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg; Orion Corporation, Finland) under fasting conditions.

**Study 3**

An open-label, randomised, four-period, two-treatment, two-sequence, replicate, crossover, single-dose bio equivalence study comparing the test product, FDC of Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg tablet (Torrent Pharmaceuticals Limited) versus the reference product, Stalevo tablets containing Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg (Orion Corporation, Finland) in healthy human volunteers under fasting conditions.

Subjects were administered a single dose of either the test or reference product with 200 ml of water at room temperature after at least an 8-hour overnight fast, according to the randomisation schedule. Blood sampling was performed pre-dose and up to 12 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below:

### Evaluation of bioequivalence

**Pharmacokinetic parameters (geometric Least Square Mean [LSM] ratios and confidence intervals [CI] for levodopa, carbidopa and entacapone**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Mean Ratio Test/Ref</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levodopa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>104.44</td>
<td>99.94 – 109.14</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>97.33</td>
<td>93.76 – 101.03</td>
</tr>
<tr>
<td><strong>Carbidopa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>106.41</td>
<td>98.55 – 114.90</td>
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<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>105.47</td>
<td>98.21 – 113.27</td>
</tr>
<tr>
<td><strong>Entacapone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>101.52</td>
<td>91.32 – 112.86</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>102.97</td>
<td>99.94 – 106.10</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to $t$ hours  
$C_{\text{max}}$ maximum plasma concentration

**Bioequivalence Discussion and Conclusion**

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for $C_{\text{max}}$ and AUC values.

The intra-subject coefficient of variance (%ISCV) of the reference formulation for the pharmacokinetic parameter of $C_{\text{max}}$ was ≤ 30% for levodopa and >30% for carbidopa and entacapone. Hence, for the bioequivalence claim, the two one-sided tests procedure was used for levodopa and scaled average bioequivalence procedure was used for carbidopa and entacapone for bioequivalence claim.
The results of the study demonstrate that the AUC$_{(0-t)}$ and $C_{\text{max}}$ values for levodopa, carbidopa and entacapone lie within the acceptance limits. Hence the data from this study support the claim that the applicant’s test product (FDC of Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg tablet; Torrent Pharmaceuticals Limited) is bioequivalent to the reference product, Stalevo tablets (containing Levodopa 50mg, Carbidopa 12.5mg and Entacapone 200mg; Orion Corporation, Finland), under fasting conditions.

**Overall Bioequivalence Conclusion**

Based on the results from Study 2 and Study 3, bioequivalence has been demonstrated between the applicant’s test products FDC of Levodopa 200mg, Carbidopa 50mg and Entacapone 200mg tablet and Levodopa 50mg, Carbidopa 12.5mg and Entacapone 200mg tablet and the reference products Stalevo tablets (containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg; Orion Corporation, Finland) and Stalevo tablets (containing Levodopa 50mg, Carbidopa 12.5mg and Entacapone 200mg; Orion Corporation, Finland), respectively, under fasting conditions.

The results of the studies with FDC of Levodopa 200mg, Carbidopa 50mg and Entacapone 200mg tablet and Levodopa 50mg, Carbidopa 12.5mg and Entacapone 200mg tablet, can be extrapolated to other tablet strengths, 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg /200 mg and 150 mg/37.5 mg/200 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

**IV.2 Pharmacodynamics**

The clinical pharmacology of levodopa, carbidopa and entacapone is well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

**IV.3 Clinical Efficacy**

The clinical pharmacology of levodopa, carbidopa and entacapone is well-known. No new efficacy data are presented for these applications and none are required.

**IV.4 Clinical Safety**

With the exception of the data generated during the bioequivalence studies, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence studies.

**IV.5 Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levodopa, Carbidopa and Entacapone Accord film-coated tablets.

A summary of safety concerns in listed in the table below:
IV.6 Clinical Expert Report (Clinical Overview)
A clinical overview written by an appropriately qualified physician has been provided and is a suitable summary of the clinical aspects of the dossier.

IV.7 Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable from a clinical perspective. The SmPCs are consistent with those for the innovator products. The PIL is consistent with the details in the SmPCs and in line with the current guidance. The labelling is in line with current guidance.
IV.8 Conclusion
It is recommended that Marketing Authorisations are granted for Levodopa/Carbidopa/Entacapone Accord film-coated tablets, from a clinical point of view.

V. 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 pack leaflet was English.

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.

IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Levodopa/Carbidopa/Entacapone Accord 100 mg/25 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 200 mg/50 mg/200 mg, 50 mg/12.5 mg/200 mg and 75 mg/18.75 mg/200 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of levodopa, carbidopa and entacapone are well-known, no additional data were required.

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s test products FDC of Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg tablet and Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg tablet and the reference products, Stalevo tablets containing Levodopa 200 mg, Carbidopa 50 mg and Entacapone 200 mg (Orion Corporation, Finland) and Stalevo tablets containing Levodopa 50 mg, Carbidopa 12.5 mg and Entacapone 200 mg (Orion Corporation, Finland), respectively, under fasting conditions.

A biowaiver has been granted to the applicant’s fixed drug combination 75 mg/18.75 mg/200 mg, 100 mg/25 mg/200 mg, 125 mg/31.25 mg/200 mg and 150 mg/37.5 mg/200 mg strength tablets based on data presented, in line with the current bioequivalence guideline.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for these applications. As the safety profiles of levodopa, carbidopa and entacapone is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence studies.
PRODUCT LITERATURE
The SmPCs and PIL are satisfactory, and consistent with those for the cross-reference products. The labelling complies with statutory requirements and is satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levodopa, carbidopa and entacapone is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk balance is therefore considered to be positive.

RECOMMENDATION
The grant of Marketing Authorisations is recommended.
Annex 1

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>