EMA/52316/2011
Committee for medicinal products for human use (CHMP)

Assessment Report
For
Entacapone Teva
(entacapone)

Procedure No.: EMEA/H/C/002075

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 6 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Entacapone Teva, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product', of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2009.

The applicant applied for the following indication "as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations".

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC, as amended.

The chosen reference product is: Comtess

■ Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Comtess 200 mg film-coated tablets
- Marketing authorisation holder: Orion Corporation, Finland
- Date of authorisation: 16-09-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/082/001-003, EU/1/98/082/005

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Comtess 200 mg film-coated tablets
- Marketing authorisation holder: Orion Corporation, Finland
- Date of authorisation: 16-09-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/082/001-003, EU/1/98/082/005
- Member State of source: United Kingdom
- Bioavailability study number(s): Protocol number P1EB09005

The Rapporteur appointed by the CHMP was Tomas Salmonson.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 6 May 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2010.
- During the meeting on 20-23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 September 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 November 2010 and an updated Assessment Report on 16 November 2010.
- During the meeting on 15-18 November 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Entacapone Teva on 18 November 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 18 February 2011.

2 Scientific discussion

2.1 Introduction

Entacapone Teva is indicated as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations

Entacapone functions as a catechol-O-methyl transferase inhibitor therefore decreasing in the periphery the metabolic loss of levodopa to 3- methoxy-4-hydroxy-L-phenylalanine (3-OMD), which does not easily cross the blood brain barrier. This leads to a higher levodopa AUC. The amount of levodopa available to the brain is increased. Entacapone thus prolongs the clinical response to levodopa. It is used in the treatment of Parkinson's disease: when administered in conjunction with dopaminergic agents such as L-DOPA.

One 200 mg tablet is taken with each levodopa/dopa decarboxylase inhibitor dose. The maximum recommended dose is 200 mg ten times daily, i.e. 2,000 mg of entacapone.

Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the COMT enzyme.

Entacapone Teva 200 mg is a generic 200 mg film-coated tablet packaged in HDPE bottles with PP screw caps and with desiccant insert. Entacapone Teva is a generic of the centrally authorised Comtess 200 mg film-coated tablets.

The efficacy and safety of entacapone has been demonstrated in several controlled studies. A summary of these studies can be found in the EPAR of the reference product Comtess.

The reference product was authorized in the Community on 16th September 1998 for Orion Corporation. Bioequivalence to the reference product from the United Kingdom market was demonstrated.

2.2 Quality aspects

2.2.1 Introduction

Entacapone Teva is presented as film-coated tablet, containing 200 mg of entacapone as the active substance.

Other ingredients are defined in the SPC section 6.1.

The tablets are packaged in HDPE bottles with PP screw caps and with desiccant insert.

2.2.2 Active Substance

The active substance of Entacapone Teva is entacapone, which has the chemical name: (2E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethylprop-2-enamide. It corresponds to the molecular formula $C_{14}H_{15}N_3O_5$ and relative molecular mass of 305.29. It appears as yellow non-hygroscopic crystalline powder, practically insoluble in water, soluble or sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

Entacapone exhibits polymorphism as per the available literature. However based on the XRD spectra it is found that, entacapone manufactured by the active substance supplier is consistent regarding the polymorphic form.

Manufacture

An ASMF has been submitted for the drug substance. The drug substance synthesis is described in three steps. Entacapone from the last step is then purified to give the desired crystalline form. Detailed information regarding the control of starting materials, reagents and raw materials as well as the control of critical steps and intermediates is provided in the ASMF.
Satisfactory information on the validation production batches and on the manufacturing process development is also provided.

Specification

Entacapone was not described in the European Pharmacopoeia (Ph. Eur) at the time of submission. The specification of the active substance as set up by the drug product manufacturer includes tests and limits for description (visual), identification (IR, XRPD), loss on drying, residue on ignition, heavy metals, assay (potentiometry), related substances (HPLC), residual solvents (GC), particle size distribution (laser light diffraction), bulk and tapped density (Ph.Eur.) and microbiological quality (Ph.Eur.).
Batch analysis data is presented for five batches. All data comply with the specifications.

Stability

Three validation batches have been subjected to stability studies under accelerated, long term and intermediate conditions. Results for 24 months long-term and for six months accelerated have been presented for the three batches as per ICH guidelines and no abnormality observed in either condition.

Twelve months results from the intermediate stability study have been submitted for the three batches as per ICH guidelines and no abnormality observed. All data meet the specification limits (also the tighter) in all three storage conditions and at all time points. No trends were observed.

Based on the forced degradation studies, only one degradation impurity formed or increased. However the extent of the formation / increase was found to be very marginal for the physical degradation conditions, which simulates the stability of the product. Hence, no concern with regard to the stability of the product over a long period is expected.

A photo stability study has been conducted on entacapone and it was found that no change in impurity profile was observed due to UV and fluorescent light.

In view of all the information presented, the proposed retest period and storage conditions are considered acceptable.

In accordance with EU GMP guidelines [1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3 Medicinal Product

Pharmaceutical Development

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

The aim of the development work was to formulate immediate-release tablets containing qualitatively and quantitatively the same active substance as the original product Comtess 200 mg film-coated tablets and exhibiting the same bioavailability.

The excipients selected are all standard and commonly used in the pharmaceutical industry. Most of them are also present in the formulation of the innovator product. Therefore they are expected to be compatible.

Because entacapone is practically insoluble in water and especially in low pH and highly soluble in higher pH it can be considered as a drug with low solubility according to the Biopharmaceutical Classification System, BCS. The permeability of the drug is also low; therefore, entacapone belongs to BCS class 4.
Dissolution profiles of Entacapone Teva 200 mg film-coated tablets and the reference product Comtess 200 mg film-coated tablets were tested in water an in a range of pH and buffered media. In the chosen dissolution medium sink condition was fulfilled. In this medium a very fast dissolution rate was achieved for all products tested. Therefore it can be concluded that dissolution is not a rate-limiting step.
Comparative dissolution profiles were presented between the test product and the reference product used in the bioequivalence study.

During the first set of experiments, different manufacturing processes were compared, and different excipients were added in order to find a suitable matrix for compression and dissolution. Preliminary stability studies were run with some of these batches and the results were favourable.

The final formulation was optimised in order to ensure robustness and reproducibility of the manufacture.

Based on this development work two pilot batches were manufactured for the biostudy and stability studies.

The tablets are packaged in HDPE tablet containers with screw caps of polypropylene (PP). The screw caps are stated to be tamper-evident and have a desiccant insert.

Adventitious agents

None of the excipients are of human or animal origin. Appropriate TSE/BSE free declarations were provided.

Manufacture of the Product

The manufacturing process is a standard process divided into six main steps. The critical steps have been identified and appropriate in-process controls have been set up. The holding times are defined. The manufacturing process has been adequately described and validated. The manufacturing process will be validated according to a process validation protocol on three consecutive production batches. The protocol has been presented and is found acceptable.

Product Specification

The finished product release and shelf-life specifications includes tests and limits for description (visually), identification of drug substance (UPLC, UV), identification of coating colorants (colour

reaction), uniformity of dosage units (Ph.Eur.), related substances (UPLC), dissolution (UPLC, Ph.Eur.), assay (UPLC), and microbiological quality (Ph.Eur.- non routinely).
Batch analysis data is presented for two commercial scale batches. All data presented complies with the specification and indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the Product

Long-term (25 ± 2 °C / 60 ± 5% RH) stability data for two pilot batches covering up 16 months were provided. Stability data for two pilot batches covering six months at accelerated conditions (40 °C ± 2 °C / 75% RH ± 5% RH) were also provided.
All results were found within the specification limits at all time points up to 16 months in long term and six months in accelerated storage conditions. No trends were observed for any of the tested parameters.

In-use stability
Stability data is also presented for an in-use stability study where one batch was studied for 6 months. Appearance and dissolution did not change. Assay and degradation products did not change significantly and remained within specification limits.

Based on the stability data presented the proposed shelf life and storage conditions can be accepted for Entacapone Teva.

In general, the results support the shelf life and storage conditions as defined in the SPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4 Discussion and Conclusions on chemical, and pharmaceutical aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

No further studies are required and the applicant has justified why no such data was provided.
The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on literature searches and adequate scientific literature has been provided. The overview justifies why there is no need to generate new non-clinical pharmacology, pharmacokinetics and toxicology data. There is thus no need for conducting tests on animals.
No Environmental Risk Assessment was submitted. The introduction of Entacapone Teva manufactured by Teva Pharmaceutical Works Private Limited Company is unlikely to result in any significant increase in the combined sales volumes for all entacapone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.4 Clinical Aspects

2.4.1 Introduction

To support the application, the applicant has submitted a single bioequivalence study P1EB09005.
For the clinical assessment the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EPW/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

GCP

The bioequivalence study was performed in accordance with GCP as claimed by the applicant.
One inspection of the site has been performed by the Canadian Authority (Health Canada, Health Products and Food Program-Inspectorate on July 10, 2008) and five times by the FDA.

2.4.2 Pharmacokinetics

Methods

Study design

The bioequivalence study P1EB09005 was an open-label two dose study of test and reference product in a four-way cross-over replicate fasting state design. Either a single 200 mg dose of Entacapone or a single 200 mg dose of Comtess was administered to each subject with 240 ml of water following an overnight fast of at least 10 hours. The analytical personnel were blinded from the treatment sequence.
Blood sampling was performed pre-dose and then at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, and 12 hours. The washout between each of the four periods lasted for at least 7 days. The analysis was performed on the E-isomer (two stereoisomers exist) of entacapone in plasma, that stands for the majority of the AUC (95%). The stereoisomers are equally active but due to the difference in exposure, the E-isomer is the important one.
The final protocol was approved by the IRB on July 3rd, 2009 (Optimum Clinical Research Inc). A GCP statement was included.
The study was performed in Canada. The bioanalysis took place in Canada.
Test and reference products

Test Product: Entacapone 200 mg film-coated tablets

Manufacturer: Teva Pharmaceutical Works Private Limited Company

Batch Number: 0220409

Expiration date and identity compared to the one marketed: Refer to drug product stability data, quality report.

Reference Product:

Name: Comtess film-coated Tablets 200 mg

Manufacturer and MAH: Orion Corporation, Orionintie 1 FI, 02200 Espoo, Finland

Lot Number: 1223679

Date of authorisation in the EU: 1998-09-16

Country of origin: UK

Expiration date: 10/2010

Population studied

Thirty-four (Group 1) and seventy-seven (Group 2) volunteers were screened for this study.
For Group 1, thirteen (13) subjects did not participate for the following reasons: 3 standbys and 1 overnight standby were not used. 1 subject was excluded at Period 1 check-in due to positive drug test. 3 subjects were not available for the study. 5 subjects were withdrawn, because the subjects were no longer required for study as study was full.
Five (5) subjects were deemed ineligible after the medical screening for the following reasons: Recent blood donation (1 subject), Out-of-Specification BMI (1 subject), Out-of-Specification vitals (1 subject), Positive Cotinine (1 subject) and Failed labs (1 subject). 16 subjects were then remaining.
For Group 2, eighteen (18) subjects did not participate for the following reasons: 1 overnight standby was not used. 5 subjects were excluded at Period 1 check-in due to Out-of-Specification vitals. 1 subject was excluded prior to dosing due to Change in Health. 11 subjects were not available for the study.
Fifteen (15) subjects were deemed ineligible after the medical screening for the following reasons: Poor veins (4 subject), Out-of-Specification vitals (3 subject), Positive Cotinine (2 subject) and Failed labs (6 subject). 44 subjects were then remaining. Subjects who completed at least two periods were included in the pharmacokinetic and statistical analysis.
In total, sixty (36 males and 24 females) healthy non-smoking subjects aged 19-54 years were enrolled. Their races were either of Indian, Asian, Black or White origin.

Protocol Deviations

Type	Subject No. (A)	Subject No. (B)
Concomitant medications		
Study Procedure [a]	35, 37	29, 54

Treatment A (Test Product): 200mg Entacapone tablet by TEVA Pharmaceutical Works Private Limited Company, Hungary (Batch #: 0220409); Treatment B (Reference Product): Comtess® film-coated tablet by Orion Pharma Limited, UK (Lot #: 1223679)

During the 12 hour post dose vital signs at Period 3 check-out, the vital signs for some subjects were measured one minute earlier than the 12 hour +/- 1 hour window allows. This occurred for subjects 29, 35 and 37. During period 4, the 12 hour post dose blood pressure and heart rate for Subject 54 was performed, however, not documented on source in error resulting in no values for these parameters. This subject had no ongoing Adverse Events at this time and was seen by the sub-investigator prior to leaving the clinic at the end of the confinement period.
Pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times. These deviations did not have an impact on the results.

Analytical methods

The analyses to determine the human plasma concentrations of entacapone in the study samples was conducted in Canada. Plasma concentrations of entacapone (E-isomer) were determined with a High

Performance Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS) method. The analytical method was validated.

Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was adequately justified. Twenty-one samples were repeated. Long-term stability for a period covering the time from first sample collection until last sample analysis was demonstrated.
In conclusion, the CHMP considered that the performance of the analytical methods was satisfactory.

Pharmacokinetic Variables

The pharmacokinetic parameters calculated/observed were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $AUC_{0-t}/AUC_{0-\infty}$, T_{max}, Kel and $T_{1/2}$ by using standard non-compartmental methods. The primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The pharmacokinetic variables were considered to be adequate.

Statistical methods

Analysis of Variance (ANOVA) was performed on each of the pharmacokinetic parameters using SAS software. The ANOVA model containing factors for sequence of products, subjects within sequence, group, period and products was utilized in comparing the effects between the test and reference products.
A 90% confidence interval (CI) about the ratio of the mean test value to mean reference value was calculated for all of the pharmacokinetic parameters. The calculations for power and the CI used the least squares means and the standard error of the estimate, each generated with SAS software. The ratio of the geometric means for the ln-transformed data and the corresponding 90% CIs were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. According to the protocol, bioequivalence (BE) is concluded when the ratios of geometric means and their corresponding 90 % CIs are within 80-125 % for AUC_{0-t} and within 75-133 % for C_{max}. If the intra-subject variability of the reference product for C_{max} is less than 30 %, then the geometric mean ratios and their 90 % confidence intervals need to be within 80-125 % for C_{max}. T_{max} was analysed by using a non-parametric analysis.
Subjects were to be divided into two groups: Group 1 (Subject Nos. 1-16) and Group 2 (Subject Nos. 17–60) for dosing. Group 1 were to be dosed first and an interim assay and analysis were to be performed on data obtained from Group 1 for information purposes. If there were safety concerns, or if the two products were to be clearly not bioequivalent (i.e. the ratios are not indicative of BE), Group 2 was not to be dosed. Otherwise, a complete analysis of data obtained from Group 1 and Group 2 was to be performed, irrespective of the interim analysis results from Group 1. This was to be done to maintain the fixed type-I error rate at 5%. The study was not to be pre-maturely stopped if the results obtained from Group 1 meet BE. A treatment by group interaction test was performed to know if data from group 1 and 2 could be combined. Since no statistically significant treatment effect was observed, the data from both groups was pooled.
The CHMP considered the statistical approach to be acceptable since the evaluation was not stopped after group 1 based on a positive outcome (i.e. showing bioequivalence). This is acceptable from a statistical standpoint (bioequivalence was shown after the first interim analysis).

Results

Following the Group 1 interim analyses, for entacapone E-isomer, the test/reference ratios of geometric means were 102.69% (90% CI 96.70% - 109.05%) for AUC_{0-t}, 104.53% (90% CI 98.97% - 110.40%) for AUC_{0-inf}, and 103.51% (90% CI 86.14% - 124.38%) for C_{max}.
Additionally, there were no safety concerns observed during Group 1 and therefore it was decided to continue the study and dose Group 2. The pharmacokinetic parameters for group 1 and 2 combined are presented in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) of entacapone (E-isomer), group 1 and 2 combined, n=55

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	1825 (486.2)	1882 (463.1)	1437 (638.8)	1 (0.17-5)
Reference	1815 (450.4)	1826 (460.5)	1432 (593.0)	1 (0.33-4)
*Ratio (90% CI)	100.14 (97.03-103.34)	101.75 (98.93-104.65)	97.57 (89.62-106.23)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

*ln-transformed values

No sequence or period effects were observed for AUC_{0-t}, $AUC_{0-\infty}$ or C_{max}. The extrapolated area in all subjects was below 20 %. No pre-dose levels were detected. The 90 % confidence intervals for each primary parameter fall within the normal acceptance limits of 80-125 % and therefore bioequivalence with the reference product has been established.

Safety data

22 subjects experienced a total of 42 adverse events (AEs) over the course of the study. AEs were mild to moderate in intensity. Overall, the most common AEs reported were tachycardia, nausea, dizziness, headache, blood pressure increased and heart rate increased. The frequency of AEs was similar for both treatments. No subject discontinued due to an AE. No serious adverse events (SAEs) were reported over the course of this study.

The clinical portion of the study was completed without any significant sequelae attributable to the investigational drug. Overall, entacapone tablets were well tolerated as a single oral dose of 200 mg (1 × 200 mg) administered to healthy adult subjects under fasting conditions.

Conclusions

Based on the presented bioequivalence study, Entacapone Teva 200 mg film-coated tablet is considered bioequivalent with Comtess 200 mg film-coated tablet.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5 Discussion on Clinical aspects

The CHMP assessment addressed pharmacokinetic data for a single bioequivalence study (study P1EB09005). The study design is considered adequate with regard to wash-out period, sampling period and sampling scheme according to expected T_{max} and $T_{1/2}$. The CHMP considered it acceptable to demonstrate bioequivalence for the active E-isomer alone. The study was conducted in line with GCP.
The results of the bio-equivalence study show that the 90 % confidence intervals for each primary parameter fall within the normal acceptance limits of 80-125 % and therefore bioequivalence with the reference product has been established.

2.4.6 Conclusions on clinical aspects

Based on the presented bioequivalence study, Entacapone Teva 200 mg film-coated tablet is considered bioequivalent with Comtess 200 mg film-coated tablet.

2.5 Pharmacovigilance

PSUR

The PSUR submission schedule for Entacapone film-coated tablets should follow the PSUR schedule for the reference product.
The data lock point for the reference medicinal product is 16 January 2011.

Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.
The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation plan is not required.

2.6 User consultation

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet was judged acceptable.

2.7 Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality and clinical data and the bioequivalence has been shown for the 200 mg film-coated tablet. A benefit/risk ratio comparable to the reference product can therefore be concluded.
The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Entacapone Teva as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in adult patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations, was favourable and therefore recommended the granting of the marketing authorisation.