COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Entacapone Unichem 200 mg film-coated tablets (entacapone)

NL/H/4712/001/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Entacapone Unichem 200 mg film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/4939/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Entacapone Niche 200 mg film-coated tablets (entacapone)

Procedure No: UK/H/4939/DC

UK Licence No: PL 19611/0183

Niche Generics Limited

LAY SUMMARY

On 21 November 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Niche Generics Limited for the medicinal product Entacapone Niche 200 mg film-coated tablets (PL 19611/0183; UK/H/4939/001/DC). This medicine is only available on prescription from your doctor and is used together with levodopa to treat Parkinson's disease. Entacapone Niche film-coated tablets improve the therapeutic effect of levodopa in relieving the symptoms of Parkinson's disease. Entacapone Niche film-coated tablets have no effect on relieving the symptoms of Parkinson´s disease unless taken with levodopa.

The active ingredient in Entacapone Niche 200 mg film-coated tablets is entacapone, which belongs to a group of medicines called catechol-O-methyl transferase (COMT) inhibitors.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Entacapone Niche 200 mg film-coated tablets outweigh the risks and a Marketing Authorisation was granted.

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Module 1
Information about the initial procedure

Product Name	Entacapone Niche 200 mg film-coated tablets
Type of Application	Directive 2001/83/EEC (as amended), Article 10(1), Generic
Active Substance	Entacapone
Form	Film-coated tablets
Strength	200 mg
MA Holder	Niche Generics Limited, 1 The Cam Centre, Wilbury Way, Hitchin, Hertfordshire, SG4 0TW, United Kingdom.
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Germany, Ireland and The Netherlands
Procedure Number	UK/H/4939/001/DC
Timetable	Day 210 – 17 September 2012

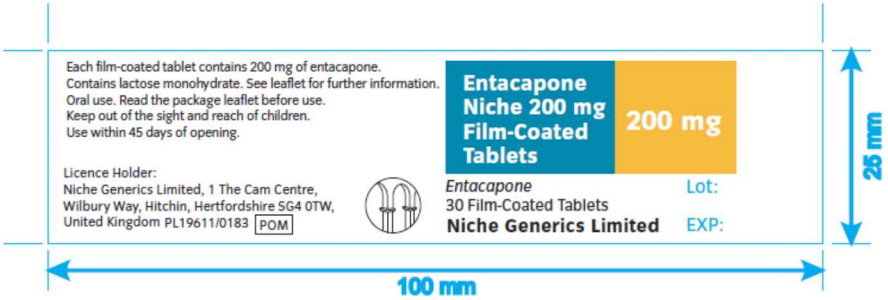
Module 2
Summary of Product Characteristics

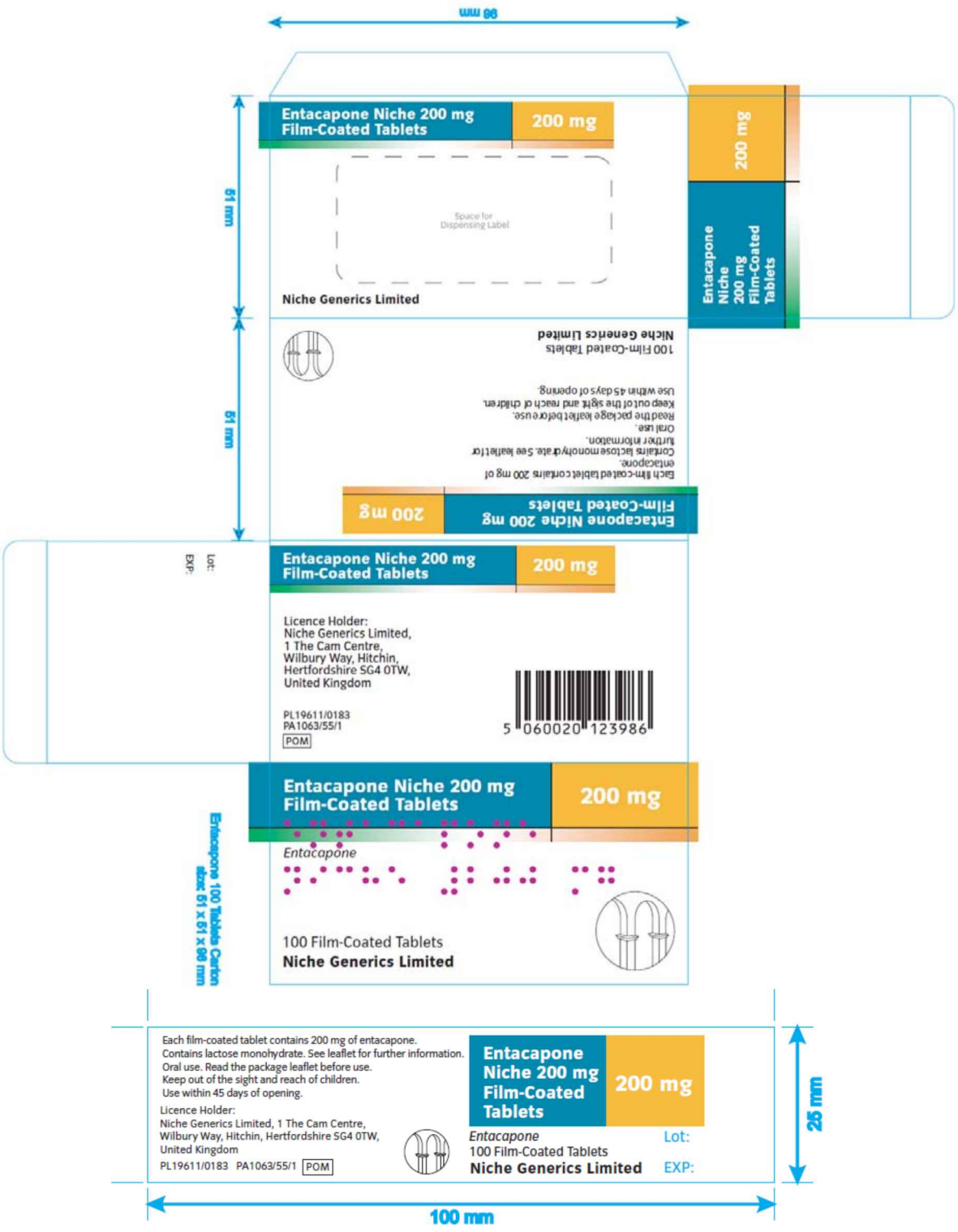
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4
Labelling




Entacapone Niche 200 mg Film-Coated Tablets
200 mg
Space for Dispensing Label
Niche Generics Limited
61 mm
61 mm
Entacapone Niche 200 mg Film-Coated Tablets
200 mg
Lot:
EXP:
Licence Holder:
Niche Generics Limited,
1 The Cam Centre,
Wilbury Way, Hitchin,
Hertfordshire SG4 0TW,
United Kingdom
PL19611/0183
PA1063/55/1
POM
5 060020 123986
Entacapone Niche 200 mg Film-Coated Tablets
200 mg
Entacapone
100 Film-Coated Tablets
Niche Generics Limited
Entacapone 100 Tablets Carton 62mm 61 x 61 x 98 mm
Each film-coated tablet contains 200 mg of entacapone.
Contains lactose monohydrate. See leaflet for further information.
Oral use. Read the package leaflet before use.
Keep out of the sight and reach of children.
Use within 45 days of opening.
Licence Holder:
Niche Generics Limited, 1 The Cam Centre,
Wilbury Way, Hitchin, Hertfordshire SG4 0TW,
United Kingdom
PL19611/0183 PA1063/55/1 POM
Entacapone Niche 200 mg Film-Coated Tablets
200 mg
Entacapone
100 Film-Coated Tablets
Niche Generics Limited
Lot:
EXP:
25 mm
100 mm

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Entacapone Niche 200 mg film-coated tablets (PL 19611/0183; UK/H/4939/001/DC) could be approved. The product is a prescription-only medicine (POM) 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.

The active ingredient, entacapone, is a reversible, specific, and mainly peripherally acting catechol-O-methyl transferase (COMT) inhibitor designed for concomitant administration with levodopa preparations. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the COMT enzyme; as a result, the amount of levodopa available to the brain is increased. Entacapone thus prolongs the clinical response to levodopa.

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Germany, Ireland and The Netherlands as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Comtess 200 mg film coated tablets (Orion Corporation, Finland) which was authorised in the EEA via the Centralised Procedure on 16 September 1998.

A single-dose, bioequivalence study was submitted to support this application, comparing the applicant's test product Entacapone 200 mg Film-Coated Tablets (Niche Generics Limited, UK) versus the reference product Comtess 200 mg film coated tablets (Orion Corporation). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP)

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has 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 this product.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer 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 RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 17 September 2012. After a subsequent national phase, a licence was granted in the UK on 21 November 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Entacapone Niche 200 mg film-coated tablets
Name of the active substance(s) (INN)	Entacapone
Pharmacotherapeutic classification (ATC code)	Other dopaminergic agents, (N04BX02).
Pharmaceutical form and strength(s)	Film-coated tablets
Reference number for the Mutual Recognition Procedure	UK/H/4939/001/DC
Reference Member State (RMS)	United Kingdom
Concerned Member States (CMS)	Germany, Ireland and The Netherlands
Marketing Authorisation Number	PL 19611/0183
Name and address of the authorisation holder	Niche Generics Limited, 1 The Cam Centre, Wilbury Way, Hitchin, Hertfordshire, SG4 0TW, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

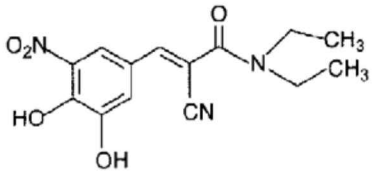
III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Entacapone

Chemical name(s): (*2E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N,N*-diethylprop-2-enamide;
(E)-α-Cyano-*N,N*-diethyl-3,4-di-hydroxy-5-nitrocinnamide;
(E)-2-Cyano-*N,N*-diethyl-3-(3,4-di-hydroxy-5-nitrophenyl) acrylamide

Structure:



Molecular formula: $C_{14}H_{15}N_3O_5$

Molecular mass 305.29

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.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely maize starch, sodium starch glycollate (Type A), colloidal anhydrous silica, povidone (K-30), polysorbate-80, mannitol, magnesium stearate and Opadry II 38G86557 Brown containing hypromellose 5 cP, lactose monohydrate, titanium dioxide (E 171), macrogol/PEG 400, macrogol/PEG 4000, talc, iron oxide yellow (E 172) and iron oxide red (E 172). Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Opadry II 38G86557 Brown and its constituents iron oxide yellow (E172) and iron oxide red (E172). Opadry II 38G86557 Brown is controlled to a suitable in-house specification. Iron oxide yellow (E172) and iron oxide red (E172) are compliant with their United States Pharmacopoeia-National Formulary specifications and are in compliance with current EU Directives concerning the use of colouring agents. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

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

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product, Comtess 200 mg film coated tablets (Orion Corporation, Finland).

Suitable pharmaceutical development data have been provided for this application. Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The tablets are packaged in white high-density polyethylene (HDPE) bottles, with white tamper proof low-density polyethylene (LDPE) closures, in pack sizes of 30, 60, 100 and 175 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

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. The data from these studies support a shelf-life of 2 years for the product stored in the unopened HPDE bottle. After first opening the HDPE bottle, the product should be used within 45 days. This medicinal product does not require any special storage precautions.

Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and, Labelling
The SmPC, PIL and labelling are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) form
The MAA form is satisfactory.

Expert report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of entacapone are well-known, no new non-clinical data have been submitted and none are required.

The applicant's 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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS

The clinical pharmacology of entacapone is well-known. With the exception of data from the bioequivalence study described below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

An open label randomised, two-treatment, two-period, two-sequence, single-dose crossover study comparing the pharmacokinetics of the test product Entacapone 200 mg Film-Coated Tablets (Niche Generics Limited, UK) and the reference product Comtess 200 mg film-coated tablets (Orion Corporation, sourced from UK) in healthy adults under fasting conditions.

The subjects were given a single dose of 200 mg of either the test or reference product with 240 ml of water, after at least a 10 hour overnight fast. Blood samples were collected before and up to 24 hours after each administration. The washout period between the treatment arms was at least 7 days. The pharmacokinetic results are presented below.

Pharmacokinetic parameters (geometric least squares mean, ratios and 90% confidence intervals [CI] of entacapone

Parameters (units)	Entacapone 200 mg (Test)	Comtess 200 mg (Reference)	Test/Ref Ratio (%)	90% CI
C_{max} (ng/mL)	1389.637	1370.275	101.41	90.26-113.94
AUC_{0-t} (ng.h/mL)	1625.960	1519.559	107.00	99.72-114.82
AUC_{0-inf} (ng.h/mL)	1686.962	1604.547	105.14	100.42-110.07

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
Ratios and 90% CI calculated from ln-transformed data

The 90% confidence intervals of the test/reference ratio for AUC_{0-t}, AUC_{0-inf} and C_{max} lie within the acceptable limits of 80.00% to 125.00%, in line with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product Entacapone 200 mg Film-Coated Tablets is bioequivalent to the reference product Comtess 200 mg film-coated tablets (Orion Corporation).

Efficacy

The efficacy of entacapone is well-known. No new efficacy data have been submitted and none are required for applications of this type.

Safety

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

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person

responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL), Labels

The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and is in-line with the current guidelines. The labelling is in line with the current guidelines.

Clinical Expert Report (Clinical Overview)

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Entacapone Niche 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 and none are required for an application of this type.

EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant's Entacapone 200 mg film-coated tablets and the reference product Comtess 200 mg film-coated tablets (Orion Corporation).

SAFETY

With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of entacapone is well-known, no additional data were required.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome