CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Encapia 200 mg, film-coated tablets Medochemie Limited, Cyprus

entacapone

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2497/001/DC
Registration number in the Netherlands: RVG 111101

24 June 2013

Pharmacotherapeutic group:	other dopaminergic agents
ATC code:	N04BX02
Route of administration:	oral
Therapeutic indication:	as 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
Prescription status:	prescription only
Date of authorisation in NL:	10 April 2013
Concerned Member States:	Decentralised procedure with BG, CY, EE, RO
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Encapia 200 mg, film-coated tablets containing entacapone from Medochemie Limited. The date of authorisation was on 10 April 2013 in the Netherlands.

The product 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.

A comprehensive description of the indications and posology is given in the SPC.

Entacapone belongs to a new therapeutic class, catechol-O-methyl transferase (COMT) inhibitors. It is a reversible, specific, and mainly peripherally acting COMT inhibitor designed for concomitant administration with levodopa/DOPA decarboxylase inhibitor combined preparations. Entacapone decreases the metabolic loss of levodopa to 3-O-methyldopa (3-OMD) by inhibiting the COMT enzyme. 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.
Entacapone inhibits the COMT enzyme mainly in peripheral tissues. COMT inhibition in red blood cells closely follows the plasma concentrations of entacapone, thus clearly indicating the reversible nature of COMT inhibition.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Comtan 200 mg film-coated tablets which has been registered in the EEA by Novartis Europharm Ltd. since 22 September 1998 (EU/H/1/98/081/001-004).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Comtan 200 mg tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is entacapone, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a greenish-yellow or yellow powder, which is practically insoluble in water, soluble or sparingly soluble in acetone and slightly soluble in anhydrous ethanol. Entacapone exhibits cis/trans isomerism and polymorphism. The drug substance used is the E-isomer and polymorphic form A.

The CEP procedure is used for the active substance by both manufacturers. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is generally in line with the Ph.Eur. monograph, with additional requirements for particle size distribution and residual solvents. The requirements for residual solvents are in line with those of the active substance suppliers. The drug substance specification is acceptable.
Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance from one manufacturer is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
For the second CEP holder, stability data on the active substance have been provided for three full-scale batches stored at 30°C/65% RH (24 months) and 40°C/75% RH (6 months). All parameters remain relatively stable at both conditions. Based on the stability results provided the proposed re-test period of 36 months and the proposed storage condition ‘Store protected from light’ can be granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Encapia 200 mg is a brown, capsule-shaped, convex, film-coated tablet.

The film-coated tablets are packed in:
- Brown amber glass bottles (hydrolytic class III) with white LDPE closures and with one white cylindrical silica gel desiccant pill with a warning in red. Each bottle also includes one piece of white polyurethane foam to offer the tablets protection while transportation.

- White HDPE bottles with white LDPE closure and with one white cylindrical silica gel desiccant pill with a warning in red. Each bottle also includes one piece of white polyurethane foam to offer the tablets protection while transportation.
- PVC/PVDC-Alu opaque blisters.

The excipients are:
Tablet core - cellulose microcrystalline 102, mannitol E421, sodium starch glycolate - type A, magnesium stearate E572
Coating - hypromellose 2910 5mPa•s E464, titanium dioxide E171, macrogol 400, iron oxide yellow E172, iron oxide red E172, iron oxide black E172, talc E553b, macrogol 6000.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, comparative dissolution studies and optimising the manufacturing process.
A bioequivalence study was performed with a full-scale batch of the drug product. The batch used in the study has the same composition and is manufactured in the same way as the future commercial batches. The dissolution profiles provided are considered essentially similar, as demonstrated by comparison at three different pH values. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: pre-blending, wet granulation, drying, sifting, blending, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two production-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. or in-house requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of drug substance, identification of colorants, average mass, water content, dissolution, uniformity of dosage units (content uniformity), disintegration time, hardness, related substances, assay and microbial limits. The release and shelf-life limits are identical except for related substances, assay and water content.
The analytical methods have been adequately described and validated, and are stability indicating. Batch analytical data have been provided on three batches (two production scale, one pilot scale), demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on four batches (two pilot scale, two production scale) stored at 25°C/60% RH (24, 18 months), 30°/65% RH (12 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in amber glass bottles, PVC-PVDC/Al blister and HDPE bottles.
A slight decrease in dissolution was observed in all containers. All other parameters tested remained relatively stable throughout the test periods at both test conditions in all containers tested and within specification limits. Photostability studies, in line with ICH Q1B, were performed on two pilot-scale batches. Based on the results the applicant considers the drug product to be photostable.
Based on the stability data provided a shelf-life of 24 months without special storage conditions (glass bottle) and store below 30°C (HDPE bottle and blister) can be granted.
Stability data has been provided demonstrating that the product remains stable for 33 days in both glass containers following first opening of the container, when stored without special storage conditions. Given the posology a declaration of an in-use shelf life is not considered necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Magnesium stearate is the only excipient that may be of animal origin. Magnesium stearate is obtained form two sources. Magnesium stearate from the first source is of vegetable origin. A CEP has been provided for magnesium stearate from the second source declaring complies with the Ph.Eur. with respect to TSE/BSE safety.

II.2 Non-clinical aspects

This product is a generic formulation of Comtan 200 mg, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of entacapone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Entacapone is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Encapia 200 mg (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Comtan 200 mg film-coated tablets (Novartis Europharm Ltd, UK) obtained from Greece.

The choice of the reference product
The choice of the reference product in the bioequivalence study is accepted, as the product has been registered through a centralised procedure.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, 4-way replicated, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects (9 females and 17 males), aged 19-33 years. Each subject received a single dose (200 mg) of one of the 2 entacapone formulations. The tablet was orally administered after an overnight fast of at least 8 hours. There were 4 dosing periods, each separated by a washout period of 7 days.

Blood samples were collected pre-dose and 0.16, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, and 10 hours collection after administration of the products. The study design is acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 26 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of entacapone under fasted conditions.

Treatment N=	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2347 ± 737	2403 ± 741	2114 ± 1065	0.75 0.16 – 5.0	0.55 ± 0.21
Reference	2203 ± 652	2309 ± 648	1884 ± 1218	1.13 0.16 – 4.0	0.64 ± 0.28
***Ratio (90% CI)**	1.03 (0.99-1.07)	0.95 (0.89-1.00)	1.17 (1.02-1.37)	--	--
CV (%)	11.9	20.0	47.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and $AUC_{0-\infty}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25.
Widened acceptance criteria of 69.8-143.19% are applied for $C_{max,}$ as the intra-subject variability was more than 30%. The ratio is within this pre-defined acceptance range with a mean of 117%.
Based on the pharmacokinetic parameters of entacapone under fasted conditions, it can be concluded that Encapia 200 mg and Comtan 200 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Entecapone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of desloratadine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Safety
A total of 12 adverse events (AE) were reported: 9 during the conduct of the study and 3 during follow-up. Six adverse events were reported in 6 subjects who had received the reference product and 3 adverse events were reported in 2 subjects who had received the test product during the conduct of the study. Three AEs from 2 subjects were reported during the follow-up period. All the adverse events reported were mild to moderate in nature.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Entacapone was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of entacapone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Comtan.

Readability test
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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question meets the criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Encapia 200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Comtan 200 mg film-coated tablets. Comtan is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Encapia 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 March 2013. Encapia 200 mg, film-coated tablets was authorised in the Netherlands on 10 April 2013.

The date for the first renewal will be: 14 March 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached