CBG MEB

Public Assessment Report

Scientific discussion

Carbidopa/Levodopa Bristol 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg tablets

(carbidopa/levodopa)

NL/H/3044/001-004/DC

Date: 25 February 2015

This module reflects the scientific discussion for the approval of Carbidopa/Levodopa Bristol 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg tablets. The procedure was finalised on 8 October 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Carbidopa/Levodopa Bristol 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg tablets from Bristol Laboratories Ltd.

The product is indicated for treatment of Parkinson's disease.

The product is a combination of levodopa and an inhibitor of dopadecarboxylase particular used in patients treated with levodopa alone who showed motor fluctuations. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sinemet. The first authorisation in the EEA was obtained in the UK by Merck Sharp & Dohme for Sinemet 12.5 mg/50 mg tablets in 1988, for Sinemet 10/100 mg tablets in 1973, for Sinemet Plus 25 mg/100 mg tablets in 1981 and for Sinemet 25 mg/250 mg tablets in 1973.
The innovator products in the Netherlands are Sinemet 62.5 mg tablets (NL License RVG 12858), Sinemet 110mg tablets (NL RVG 06706), Sinemet 125mg tablets (NL RVG 08740) and Sinemet 275 mg tablets (NL RVG 06707), registered by Merck Sharp & Dohme BV.

The concerned member states (CMS) involved in this procedure were Germany (25 mg/100 mg and 25 mg/250 mg), Malta (10 mg/100 mg, 12.5 mg/100 mg and 25 mg/250 mg), Spain (25 mg/100 mg and 25 mg/250 mg) and the United Kingdom (all strengths).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Carbidopa/Levodopa Bristol 10 mg/100 mg is a light blue coloured, oval shaped scored tablet with C and break line on one side and 18 on other side.
Carbidopa/Levodopa Bristol 12.5 mg/50 mg is a light yellow coloured, oval shaped scored tablet with C and break line on one side and 17 on other side.
Carbidopa/Levodopa Bristol 25 mg/100 mg is a yellow coloured, oval shaped scored tablet with C and break line on one side and 19 on other side.
Carbidopa/Levodopa Bristol 25 mg/250 mg is a light blue coloured, oval shaped scored tablet with C and break line on one side and 20 on other side.

The tablets can be divided into equal halves.

The tablets are packed in Alu-Alu blisters.

The excipients are: crospovidone, magnesium stearate, microcrystalline cellulose, pre gelatinised starch (maize), Indigo carmine lake (E132) (10/100 mg and 25 mg/250 mg), Quinoline Yellow lake (E104) (12.5/50 mg and 25/100 mg).

The 12.5/50 mg tablet and the 25/100 mg tablet are fully dose proportional and the 10/100 mg tablets and the 25/250 mg tablets are also fully dose proportional.

II.2 Drug Substances

Carbidopa
The first active substance is carbidopa, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellowish-white crystalline powder, and

is slightly soluble in water. Carbidopa contains one chiral centre. The drug substance is the pure S enantiomer. No polymorphism has been reported.

The CEP procedure is used for both manufacturers of the active substance. 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 in line with the Ph.Eur. with additional requirements for related substances, residual solvents, particle size and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the respective drug substance specification have been provided for one full-scale batch from each source.

Stability of drug substance
The active substance 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.
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (35 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided the proposed re-test period of 35 months can be granted when stored in the original package in order to protect from light.

Levodopa
The second active substance, levodopa, is an established active substance described in the Ph.Eur. The active substance is a white to almost white crystalline powder, and is slightly soluble in water. Levodopa contains one chiral centre. The drug substance is the pure S enantiomer. No polymorphism has been reported. For this drug substance the CEP procedure is used.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is line with the Ph.Eur. monograph and the CEP with acceptable additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided the proposed re-test period of 30 months can be granted when stored in the original package in order to protect from light.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials and dissolution trials. Formulation trials were performed to investigate the effect of the addition of a disintegrant and the level of the disintegrant, the milling method, the addition of a binder on the dissolution profile and flow properties. The choice of manufacturing process and packaging has been adequately justified.

The 25/250 mg batch and the 25/100 mg batch used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The bioequivalence batches are of sufficient size in relation to the intended commercial batch size. The studies were performed against the UK reference products. The dissolution profiles of the batches used in the bioequivalence study are considered similar at all pH tested.
Certificates of analysis has been provided for each strength indicating that the batches comply with the requirements for the subdivision of tablets described in the Ph.Eur. monograph for tablets.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: wet granulation, blending and compression. The product is manufactured using conventional manufacturing techniques.
Adequate process validation data of three pilot batches of each strength has been provided. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with relevant Ph.Eur. monographs, except for indigo carmine lake and quinoline yellow lake which comply with the in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average mass, uniformity of mass, disintegration time, dimension, hardness, water content, dissolution, uniformity of dosage units, related substances, hydrazine assay and microbial quality. The release and shelf-life limits are identical with the exception of related substances. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three pilot-scale batches of each strength stored at 25°C/60% RH (12 months) and 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 Al/Al blisters.
The same trends were observed in all batches at both conditions. The photostability data provided show that storage in the original package is not necessary.
Based on the stability data provided the proposed shelf life of 24 months without special storage conditions can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin. A declaration of the origin of magnesium stearate has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Carbidopa/Levodopa Bristol 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to perform process validation on the first three production scale batches.
- The MAH committed to continue the long term stability studies for the drug substance carbidopa.
- The MAH committed to continue the long term stability studies for the drug substance levodopa.
- The MAH committed to continue the ongoing long-term stability studies for the drug product as per provided study design (i.e. up to 36 months).
- The MAH committed to include the first three production-scale batches of the maximum batch size of each strength in accelerated and long-term stability studies.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sinemet, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levodopa and carbidopa are well-known active substances 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Carbidopa/Levodopa Bristol 25/250 mg (Bristol Laboratories Ltd, UK) is compared with the pharmacokinetic profile of the reference product Sinemet® 25/250 mg tablets (Merck Sharp & Dohme Limited, UK).
In addition a bioequivalence study was conducted with Carbidopa/Levodopa Bristol 25 mg/100 mg (Bristol Laboratories Ltd, UK) versus Sinemet Plus 25 mg/100 mg tablets (Merck Sharp & Dohme Limited, UK).

The choice of the reference products in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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

Biowaiver
The 25 mg/250 mg strength and 10 mg/100 mg strength are dose-proportional, as well as the 12.5/50 mg tablet and the 25/100 mg tablet. All criteria for granting a biowaiver have been fulfilled. Therefore the results obtained in the bioequivalence studies with the 25/250 mg and 25/100 mg strengths can be extrapolated to the other strengths.

Bioequivalence studies

Bioequivalence study I – 25 mg/250 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 18-45 years. Each subject received a single dose (25 mg/250 mg) of one of the 2 carbidopa/levodopa formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 16 hours after administration of the products.

The innovator product can be taken with or without food. Hence, it is agreed that the study was performed under fasted conditions. The procedures followed for a fasted condition and a wash-out period of 7 days (*i.e*. at least 5 terminal half-lives to exclude carry-over effects) is also agreed.

Results

Forty (40) subjects completed the study. Fourteen (14) subjects were withdrawn/dropped out: one subject did not report for Period II and 13 subjects were discontinued by the investigator due to adverse events (vomiting) in Period 1 (6 from test and 7 from reference).

The blood samples of the withdrawn/dropped- out subjects were analyzed but not included in the statistical analysis. This is in accordance with the applicable guideline.

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

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	158 ± 81	166 ± 81	40.4 ± 24	3.0 (0.8 – 6)	1.8 ± 0.4
Reference	155 ± 67	165 ± 67	40.1 ± 21	2.5 (0.8 – 6)	1.7 ± 0.5
***Ratio (90% CI)**	0.99 (0.91 – 1.08)	--	0.98 (0.90 – 1.08)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levodopa under fasted conditions.

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5667 ± 1126	5714± 1139	2154 ±598	1.8 0.3 – 5	1.6 ± 0.1
Reference	5699 ± 1117	5746 ± 1121	2380 ± 740	1.3 0.3 – 5	1.6 ± 0.2
***Ratio (90% CI)**	1.00 (0.96 – 1.03)	--	0.92 (0.82 – 1.02)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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*

Safety

A total of 19 adverse events were reported in 19 subjects during the entire duration of the study: 7 vomiting, 2 dizziness and 2 nausea cases considered probably related to the oral administration of Sinemet® 25/250 mg tablets; 6 vomiting, 1 dizziness and 1 nausea cases considered probable related to the oral administration of Carbidopa/Levodopa Bristol 25/250 mg tablets. Overall, the test and reference drugs were well tolerated.

Bioequivalence study II – 25 mg/100 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, with a mean age of 30 years. Each subject received a single dose (25 mg/100 mg) of one of the 2 carbidopa/levodopa formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00 and 16.00 hours after administration of the products.

The procedures followed for a fasted condition and a wash-out period of 8 days (*i.e*. at least 5 terminal half-lives to exclude carry-over effects) are agreed.

Results

Fifty subjects were dosed in period I and 48 subjects were dosed in period II. Two subjects were withdrawn in period-I as they met the withdrawal criteria, i.e. vomiting at or before 2 times the median Tmax of carbidopa and levodopa in any period. One subject was voluntarily withdrawn in period-II and had missed two samples. As per protocol these three subjects were not considered for statistical analysis. Plasma concentrations of 47 subjects were included in pharmacokinetic analysis of carbidopa and levodopa.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbidopa under fasted conditions.

Treatment N=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	166.6 ± 79	175.2 ± 80**	44.0 ± 18	2.5 (0.50-6.00)	--
Reference	176.3 ± 96	185.1 ± 98***	48.3 ± 27	2.5 (1.00-6.00)	--
***Ratio (90% CI)**	0.98 (0.86-1.11)	-	0.98 (0.86-1.11)	-	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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*

***N=46, ***N=45*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levodopa under fasted conditions.

Treatment N=47	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2006.4 ± 452	2040.3 ± 452	1051.8 ± 420	0.5 (0.33-2.50)	--
Reference	2125.0 ± 409	2157.0 ± 410	1103.4 ± 447	0.75 (0.33-2.5)	--
***Ratio (90% CI)**	0.93 (0.86-1.00)	--	0.95 (0.86-1.04)	-	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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*

Safety
All the subject's vital signs were within normal range. Two of forty nine subjects experienced a total of two adverse events (4.08%) after administration of single dose of test product, and two of forty nine subjects experienced two adverse events (4.08%) after administration the reference product. No serious adverse events were reported during the entire duration of the study.

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence studies Carbidopa/Levodopa Bristol 25 mg/250 mg and 25 mg/100 mg are considered bioequivalent with Sinemet 25 mg/250 mg and Sinemet Plus 25 mg/100 mg tablets respectively.

The MEB has been assured that the bioequivalence studies have 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).

IV.3 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 Carbidopa/Levodopa Bristol.

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Concomitant use of monoamine oxidase inhibitors	The risks associated with the concomitant use of monoamine oxidase inhibitors are described in the SmPC, and appropriate advice is provided to the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	prescriber to minimise these risks.	
Use in patients with glaucoma	The risks associated with the use of the drug product in patients with glaucoma are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with suspicious undiagnosed skin lesions or a history of melanoma	The risks associated with the use of the drug product in patients with suspicious undiagnosed skin lesions or a history of melanoma are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	none
Use in patients with mental disorders	The risks associated with the use of the drug product in patients with mental disorders are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Dyskinesia	The risks of dyskinesia associated with the use of the drug product is described in the SmPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with cardiovascular disorders	The risks associated with the use of the drug product in patients with cardiovascular disorders are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Laboratory test interference	The risk of laboratory test interference associated with the use of the drug product is described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risks		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with pulmonary disease; bronchial asthma; renal, hepatic or endocrine disease; and history of peptic ulcer disease or convulsions	The risks associated with the use of the drug product in patients with pulmonary disease; bronchial asthma; renal, hepatic or endocrine disease; and history of peptic ulcer disease or convulsions are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Somnolence	The risk of somnolence and episodes of sudden sleep onset associated with the use of the drug product are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients receiving general aneasthethesia	The risks associated with the use of the drug product in patients receiving general aneasthethesia are described in the SmPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Important missing information		
Use in pregnancy and breastfeeding	The SmPC states that no information is available regarding the use of drug product during pregnancy and breastfeeding, and suggests that drug product should be used during pregnancy and breastfeeding only if anticipated benefits outweigh the risks.	Not applicable
Use in patients below 18 years of age	The SmPC states that the safety of the drug product in patients under 18 years of age has not been established and its use in patients below the age of 18 years is not recommended.	Not applicable

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sinemet. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Carbidopa/Levodopa Bristol 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Sinemet 10 mg/100 mg, 12.5 mg/50 mg, 25 mg/100 mg and 25 mg/250 mg. Sinemet 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 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 Carbidopa/Levodopa Bristol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 October 2014.

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