CBG MEB

Public Assessment Report

Scientific discussion

Cortiment 9 mg, prolonged-release tablets (budesonide)

NL/H/3168/001/MR

Date: 27 August 2015

This module reflects the scientific discussion for the approval of Cortiment 9 mg, prolonged-release tablets. The mutual recognition procedure was finalised on 17 October 2014. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

AUC	Area Under the Curve
CAI	Clinical Activity Index
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned member state
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HPA (axis)	Hypothalamus-pituitary-adrenal (axis)
ICH	International Conference of Harmonisation
ITT	Intention To Treat
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MRP	Mutual Recognition Procedure
MMX	MultiMatrix (technology)
MRT	Mean retention time
OD	Once daily
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PV	Pharmacovigilance
RMS	Reference member state
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
$t_{½}$	Half-life
t_{lag}	Absorption lag time
t_{max}	Time for maximum concentration
TEAE	Treatment-Emergent Adverse Event
TID	Three times daily
TSE	Transmissible Spongiform Encephalopathy
UC	Ulcerative Colitis
UCDAI	Ulcerative Colitis Disease Activity Index
USP	Pharmacopoeia in the United States

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cortiment 9 mg, prolonged-release tablets, from Ferring B.V.

The product is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient.
A comprehensive description of the indications and posology is given in the summary of product characteristics (SmPC).

The MEB granted a marketing authorisation for the medicinal product Cortiment 9 mg on 28 February 2013. Afterwards, the Mutual Recognition Procedure (MRP) was started in order to gain marketing authorisation in several CMS. The subsequent assessment of the decentralised, national appeal and mutual recognition procedure is briefly reflected in this Public Assessment Report (PAR), in section V.

Cortiment was applied for through a hybrid application. The reference product with the same active substance is Entocort 3 mg capsules (NL license RVG 18765) which has been registered in the Netherlands by AstraZeneca B.V. since 1996 (original product).
This legal base is appropriate since Cortiment tablets do not meet the strict definition of a generic medicinal product as:

a) the quantitative composition (9 mg) of the active substance budesonide differs from that of the reference Entocort 3 mg.
b) the therapeutic indication differs.
c) bioequivalence cannot be demonstrated through bioavailability studies.
d) the pharmaceutical form differs in release characteristics.

The CMS involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

During the development scientific advice was sought in the Netherlands (September 2007, June 2010) and in Sweden (April 2007). The scientific advice concerned various aspect of the development plan.

The European Medicines Agency has waived the obligation to submit the results of studies with Cortiment tablets in all subsets of the paediatric population, as budesonide is a well known compound.

II. QUALITY ASPECTS

II.1 Introduction

Cortiment 9 mg is a white to off white, round, biconvex, film-coated tablet, debossed on one side with “MX9”. Each tablet contains 9 mg of budesonide.
The prolonged-release tablets are packed in polyamide/aluminium/PVC foil blister packs with aluminium push through foil.

The excipients are:
Tablet core - stearic acid, lecithin (soya), microcrystalline cellulose, hydroxypropyl cellulose, lactose monohydrate, colloidal hydrated silica, magnesium stearate.
Film-coating - methacrylic acid copolymer (1:1), methacrylic acid copolymer (1:2), talc, titanium dioxide, triethyl citrate.

II.2 Drug Substance

The active substance is budesonide (micronized), an established active substance described in the European Pharmacopoeia (Ph.Eur.). Budesonide is a white or almost white, crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in ethanol. The drug substance contains 9 chiral centres and is a mixture of the R and S isomers. Polymorphism was not detected during process development.

The CEP procedure is used for 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specifications are in line with the Ph.Eur., with additional requirements based on the CEP and in-house requirements for residual solvents. All specifications are acceptable. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for two development batches and three primary batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 production-scale and 3 lab- or pilot-scale batches stored at 25°C/60% RH (60 months) and 40°/75% RH (6 months). No trends or changes are seen in the tested parameters at both storage conditions. The proposed retest period of 60 months was granted. The proposed storage conditions of “store in its commercial package, at controlled room temperature and protected from light” are justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. An important feature in development was that the product is specifically designed with a colonic release for the treatment of ulcerative colitis, therefore providing slower and graded release of the active drug, with homogenous distribution throughout the colon, in the ascending, transverse, and descending sections. The MultiMatrix System (MMX) is used, a delayed and extended release technology by the application of a gastro-resistant film to a core tablet containing hydrophilic and lipophilic matrix forming substances. To ensure that the maximum level of drug substance meets the distal colon, the gastro-resistant layer must not dissolve until after the tablet leaves the stomach and first part of the small intestine. This will prevent any early drug release in the upper gastrointestinal tract. The marketing authorisation holder (MAH) performed dissolution studies to show that the drug is released only after the dissolution of the outer film at pH 7 or higher.
Several clinical studies were performed in support of this application, including a comparative bioavailability study with Entocort 3 mg capsules as reference product. The batches used in the clinical studies were manufactured according to the finalized composition and manufacturing process.
The pharmaceutical development has been described in sufficient detail.

Manufacturing process

The manufacturing process mainly consists of wet granulation and drying, blending, tabletting and film-coating. It is considered a non-standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with their Ph.Eur. or USP monographs. An additional specification for particle size is applied for micronized stearic acid. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units, assay, related substances, dissolution, dye identification, ethanol and microbiological tests. The release and shelf-life requirements are identical except for assay and total degradation products.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale primary batches, four production-scale supportive batches and on 1 pilot-scale supportive batch, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for seven production-scale batches stored at 25°C/60% RH (18 or 36 months), 30°C/65% RH (12 months), 5°C (36 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 Alu-Alu blister packs.
Stability results showed some up- and downward trends, which were however not considered significant . A photostability study was performed in conformity with ICH conditions showing that the drug product is photostable. The proposed shelf-life of 36 months and storage condition 'store below 30°C' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin and is derived from milk fit for human consumption. A TSE/BSE free certificate is provided. Magnesium stearate, stearic acid and lecithin used in the formulation are of vegetable origin and therefore free from the risk of TSE/BSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cortiment 9 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology and pharmacokinetics

Pharmacological and pharmacokinetic properties of budesonide are well known. An overview of the non-clinical properties of budesonide has been submitted. The MEB agrees that no new pharmacology and pharmacokinetic studies were required for this hybrid application.

III.2 Toxicology

A 28-day monkey bridging study was performed to compare the effects of Cortiment to the reference product Entocort. On a mg/kg basis, the doses used are in the range of the previously conducted 26 week study with budesonide (4.5 mg/kg/day for males and 6 mg/kg/day for females). Some effects were seen in this study which have been previously observed in monkeys treated with budesonide, and are likely due to

the pharmacological action of budesonide. The main issue of interest is whether the two tested compounds differ in toxicity profile compared to each other. The toxicokinetics show that exposure in monkeys was above the human exposure after treatment with 9 mg Cortiment and at this exposure no additional toxicity was seen in monkeys after treatment with Cortiment as compared to the reference compound.

Additionally, studies were performed to qualify the specification limit of 2% for one specific impurity. With regard to genotoxicity, it is agreed that this impurity has no genotoxic potential, as evidenced by negative results in two in vitro tests. The results provided justify the specification limit of 2%.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Because an increase in use can be expected, a full ERA is required. Literature references that do not contain sufficient experimental details to be assessed for validity and which do not comply with OECD guidelines are not acceptable.

Thus, according to the EMA Guideline (EMEA/CHMP/SWP/4447/00 corr 1) the following study reports should be provided for a full ERA:
- Determination of log K_{OW} according to OECD 107 or 117
- Adsorption-desorption using a batch equilibrium method (Preferably OECD 106)
- Ready biodegradability test (OECD 301)
- If not ready biodegradable, an aerobic and anaerobic transformation test (OECD 308)
- Algae, growth inhibition test
- *Daphnia sp.*, reproduction test
- Activated sludge, respiration inhibition test (already provided).

Since the compound is a potential endocrine disrupting compound, for fish a tailored risk assessment should be followed. The early life stage test is not appropriate for these compounds.See question 12 in the ‘Questions and Answers’ document (EMA/CHMP/SWP/44609/2010).

The MAH has submitted an updated ERA via variation NL/H/3168/001/II/001. This ERA is not yet complete. the MAH has committed to perform the requested studies OECD 305, OECD 218, and investigation of transformation products in study OECD 308, and submit the updated study reports in the first half of 2016.

IV. DISCUSSION ON THE NON-CLINICAL ASPECTS

This product is a hybrid formulation of Entocort which is available on the European market. Reference is made to the preclinical data obtained with the reference product. A non-clinical overview has been provided, which is based on up-to-date and adequate scientific literature. Additionally, a toxicological bridging report has been provided. The overview justifies why there is no need to generate additional non-clinical pharmacology and pharmacokinetics data. Therefore, the member states agreed that no further non-clinical studies are required.

V. CLINICAL ASPECTS

V.1 Pharmacokinetics

Budesonide is a well-known and well-characterised active ingredient. It has been marketed for over 10 years in a variety of indications. Due to this well established nature, the applicant has not conducted any hepatic metabolism and drug-drug interaction studies. Instead, the clinical pharmacology programme focused on characterising the pharmacokinetics of budesonide following administration of theprolonged-release formulations with proprietary MMX technology.

Three phase 1 studies have been conducted:
CRO-01-028 was a pharmaco-scintographic study with the objective of determining the pattern of release of budesonide from the medicinal product Cortiment.
CRO-PK-03-105 was a multiple-dose pharmacokinetics and food effect study.
CRO-PK-06-178 was a three-way, single-dose crossover study, in which pharmacokinetics of Cortiment was compared with Entocort.

Pharmaco-scintographic study CRO-01-028
In the pharmaco-scintographic study validated methods were applied for the analysis of budesonide in plasma. The methods proved to be sensitive and accurate and precise for the determination of budesonide in the matrices.

Scintigraphic data showed that release of budesonide is delayed from the Cortiment formulation, with a mean t_{lag} of about 6.8 hours. Release started in the ileum or further down in the intestinal tract. The Cortiment tablets reached the ascending colon in 6 to >24 hours. As could be expected, transit times were subject to a high variability. Mean maximal budesonide plasma concentrations were observed 14 hours after dosing. This could however also be at later time points, as in this study no blood samples were obtained between 12 and 24 hours after dosing. It was estimated that approximately 96% of the administered dose was released in the colon. The data support the availability of budesonide at the efficacy site, i.e. colon.

Pharmacokinetics and food effects study CRO-PK-03-105
This was a multiple dose pharmacokinetics and food effect study of the Budesonide MMX 9 mg tablet formulation. Twelve healthy male volunteers, aged 18 – 30 years, were included. In the multiple dose arm, subjects received the Budesonide MMX formulation once daily for 7 days. In the food interaction part, the formulation was administered under fasting conditions or after intake of a high fat, high caloric meal (about 1000 kcal, 50% fat). A 7 day washout period between the two periods was applied. Blood samples were obtained at pre-dose and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36 and 48 h post-dose. Mean pharmacokinetic budesonide data are shown in table 1.

Table 1. Mean budesonide plasma pharmacokinetic data (n = 12) after administration of a single dose of Budesonide MMX 9 mg under fasting and fed conditions.

PK parameter	Fasted conditions	Fed conditions
C_{max} (pg/ml)	1428.7 ± 1013.5	1039.9 ± 601.4
t_{lag} (h)	7.4 ± 4.2	9.8 ± 3.6
T_{max} (h)	16 ± 3.4	20.7 ± 8.7
AUC_{0-48} (pgxh/ml)	14814 ± 11254	13486 ± 9368.7
$AUC_{0-\infty}$ (pgxh/ml)	15503 ± 11340	14608 ± 9937.9
$t_{1/2}$ (h)	5.4 ± 2.0	5.6 ± 2.7
MRT (h)	19.9 ± 4.6	24.3 ± 7.1
C_{max} **maximum plasma concentration** **T_{lag}** **absorption lag time** **T_{max}** **time for maximum concentration** **AUC_{0-48}** **area under the plasma concentration-time curve from zero to 48 hours** **$AUC_{0-\infty}$** **area under the plasma concentration-time curve from time zero to infinity** **$T_{1/2}$** **half life** **MRT** **mean retention time**		

There was no indication of accumulation, but as concluded before, pharmacokinetic data are subject to a high inter subject variability.
This study showed that a high-fat, high-caloric meal did not have a statistically significant effect on AUC and C_{max}; this observation was however hampered due to a large variability in the data. The SmPC recommends intake with or without food, which is agreed.

Comparative pharmacokinetics study CRO-PK-06-178
Entocort EC was used as a comparator in Study CRO-PK-06-178. The data from this study showed that the release characteristics of Cortiment 9 mg are different than those of Entocort EC. Although systemic exposure was comparable, C_{max} was about 20% lower after administration of Cortiment 9 mg. In addition, a clear lagtime is observed while this was not the case for Entocort EC. Furthermore, t_{max} was observed almost 9 hours later for Cortiment 9 mg (13.3 vs. 4.8 hour), indicating the slower release of budesonide from the formulation. This was further supported by the slower and lower urinary excretion of the metabolite 6-β-hydroxy-budesonide.
From the same study it can be observed that after administration of a 9 mg dose, mean peak plasma concentrations are observed of about 1.3 ng/ml. The elimination half-life is about 8 hours.

Overall, pharmacokinetic results were sufficiently addressed. The available data are considered sufficient to support efficacy and safety.

The MEB has been assured that the pharmacokinetics 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).

V.2 Pharmacodynamics

No pharmacodynamic studies were performed. Budesonide is a well-known corticosteroid with topical potent anti-inflammatory and immunosuppressive effects. The exact mechanism of action of budesonide in the treatment of UC is not fully understood. In general, budesonide inhibits many inflammatory processes including cytokine production, inflammatory cell activation, and expression of adhesion molecules on endothelial and epithelial cells.

Because of the high first pass metabolism oral budesonide is in fact a topical treatment of the gut as little passes into systemic exposure. The two major metabolites (6β-hydroxy budesonide and 16α-hydroxy prednisolone) have negligible pharmacodynamic activity. Upon systemic absorption, budesonide may cause typical glucocorticoid effects.

V.3 Clinical efficacy

The clinical efficacy development program for Cortiment tablets in ulcerative colitis (UC) included two phase II studies (CRO-03-53 and CB-01-02/05) and two phase III efficacy and safety studies (CB-01-02/01 and CB-01-02/02). The clinical efficacy studies are summarized below.

Table 2. Summary of clinical efficacy studies for Budesonide MMX tablets in the treatment of mild to moderate active UC

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjects by arm ITT/ completed	Duration	% Male Mean Age (sd)	Diagnosis Incl. criteria	Primary Endpoint
CRO-03-53	10 centres: France, Belgium, Austria, Hungary	Randomized double blind two arm parallel group (I) followed by open label (II)	Budesonide MMX 9mg OD Matching placebo OD	Efficacy and safety	MMX 9mg: 18/17 Placebo: 18/15	I and II: 4 weeks each	44.5 yrs (12.6)	Left sided active mild to moderate UC, CAI score ≤14	Proportion with clinical improvement (≥50% reduction in CAI or CAI ≤4) at 4 weeks
CB-01-02/05	10 centres: Romania	Randomized double blind two arm parallel group dose finding	Budesonide MMX 3mg or 9mg, OD Placebo OD	Dose finding	MMX 3mg: 17/12 MMX 9mg: 15/11 Placebo: 17/12	8 weeks	96% male 45.0 (12.9)	Mild to moderate UC, UCDAI ≥4 and ≤10	Proportion with UCDAI defined remission and endoscopic improvement at 8 weeks
CB-01-02/01	115 centres: Canada, USA, Mexico, India	Randomized double blind, three arm parallel group	Budesonide MMX 6mg OD Budesonide MMX 9mg OD Placebo OD Asacol 2.4g TID	Efficacy and safety versus placebo	MMX 6mg: 121/72 MMX 9mg: 123/69 Placebo: 121/61 Asacol: 124/73	8 weeks	56% male 42.7 yrs (12.8)	Mild to moderate UC (UCDAI ≥4 and ≤10) Histologically confirmed	Proportion with UCDAI defined remission and endoscopic improvement at 8 weeks
CB-01-02/02	80 centres: Eastern Europe, Western Europe, Israel, Russia, Australia	Randomized double blind three arm parallel group	Budesonide MMX 6mg Budesonide MMX 9mg Matching Placebo Entocort 9mg reference arm	Efficacy and safety versus placebo	MMX 6mg: 126/ 73 MMX 9mg: 127/84 Placebo: 129/ 67 Entocort 9mg: 127/72	8 weeks	56% male 43.6 (13.7)	Mild to moderate UC (UCDAI ≥4 and ≤10) Histologically confirmed	Proportion with UCDAI defined remission and endoscopic improvement at 8 weeks
CAI: Clinical Activity Index									

ITT: Intention to Treat
MMX: Multimatrix technology
OD: Once daily
UC: Ulcerative Colitis
UCDAI: Ulcerative Colitis Disease Activity Index
TID: Three times daily

- Phase II studies

One phase II study (CB-01-02/05) was a pilot dose finding study investigating two doses of Cortiment, 3 mg and 9 mg, compared to placebo in patients with active UC of mild to moderate severity (n=49). This study supported efficacy although results appear modest (clinical remission based on Ulcerative Colitis Disease Activity Index (UCDAI)) of Cortiment 9 mg over placebo).The second study (CRO-03-53) was a preliminary efficacy and safety study of Cortiment 9 mg in patients with left sided UC of mild to moderate severity (n=36). The study did not reach the primary endpoint (based on CAI) at week 4. The study design differed from the other studies in definition of remission and patients remained on stable 5-ASA treatment.
The 9 mg dose chosen for the pivotal phase III trials is predominantly based on the effective dose of oral budesonide approved for the treatment of Crohn's disease and collagenous colitis. Whether a higher dose of Cortiment might improve efficacy results is unknown.

- Phase III studies

The two pivotal phase III clinical trials were multicentre, randomized, double-blind, and double dummy comparative studies versus placebo, with an additional reference arm. The patient population included were adult patients with active UC of mild to moderate severity (4≤ UCDAI ≤10) and confirmed by histology; patients with limited distal proctitis were excluded. Concomitant medication for the treatment of UC was not allowed. The in- and exclusion criteria are appropriate for the target population of patients with mild to moderate UC.

Both studies included two dose arms of Cortiment 9 mg and a lower dose of 6 mg to confirm the lowest effective dose. The studies were similar in design except for the active comparator arm used; Asacol 2.4 g daily in study CB-01-02/01 which was predominantly performed in the US and India and Entocort 9 mg daily in study CB-01-02/02 which was predominantly performed in Europe.
The studies lasted for 8 weeks and the objective of both studies was to demonstrate superiority of Cortiment over placebo. The lack of adequate statistical comparisons with active comparators is of concern as well-established treatments exist for patients with mild to moderate UC. In addition, critical remarks were raised on the type of comparators chosen. The use of Entocort (study CB-01-02/02) as active comparator needs justification, as it is in advance considered a suboptimal oral budesonide formulation because of the site of release of active substance. A more appropriate comparator would have been systemic oral corticosteroids, which are recommended in clinical practice in patients not responding adequately to 5-ASA[1]. The use of Asacol as an active comparator arm (study CB-01-02/01) was justified although the use of Asacol implies a different target population (first-line use, treatment-naïve population). The MAH initially proposed a systemic oral corticosteroid (methyl-prednisolone) as active comparator, but this was changed based on a meeting with the FDA, which considered that treating patients with prednisolone for eight weeks might result in excessive steroid exposure. Based on FDA advice a placebo arm was included and 5-ASA as active comparator, which is also used to induce remission following relapse of the disease. Whether steroid exposure after systemic dosing would be considered excessive depends on the type of patient population included, and the Board considered it acceptable in patients failing 5-ASA. Nevertheless, as various treatment modalities are available, the Board prefers to have a demonstration of comparable efficacy to currently established treatment. The limitations of Entocort were known to the MAH, but their primary focus was on demonstrating superiority over placebo. An increased efficacy of Cortiment over Entocort could support the rationale behind the new MMX formulation.
The primary endpoint clinical remission was defined as UCDAI score of ≤ 1, with a score of 0 for rectal bleeding and stool frequency, normal mucosa and a ≥ 1-point reduction in the endoscopic score. The primary endpoint is acceptable; however, inclusion of an endoscopic score and no mucosal friability may result in a rather strict remission criterion. Major secondary endpoints were clinical improvement, defined as a ≥ 3-point improvement in UCDAI from baseline to Visit 5/Week 8 and endoscopic improvement defined as a ≥ 1-point improvement in the mucosal appearance from baseline to Visit 5/Week 8. These endpoints are commonly used and acceptable.

In general, the baseline demographic and disease characteristics were comparable between treatment groups and between both pivotal studies. The mean age of patients in the ITT population was 43 years and half were female. About two-third of the patients had moderate disease severity and 20%-40% had extensive disease. This population seems to be in accordance with the population that might be treated with steroids. More than 50% of the patients received mesalazine or sulphasalazine prior to start of treatment.

[1] Travis SPL, et al. European evidence-based Consensus on the management of ulcerative colitis: Current management. Journal of Crohn's and Colitis (2008) 2, 24–62.

The percentage of patients on 5-ASA at screening varied between 52% (Cortiment 9 mg) and 65% (Cortiment 6 mg) within study CB-01-02/01, and between 64% (Cortiment 9 mg) and 69% (Entocort) within study CB-01-02/02. Almost all patients (92%- 95%) used a daily dose ≤ 5 g. The proportion of patients on high dose 5-ASA (4 to 5 g/day) and those on low dose 5-ASA (2 to 3.5 g) is not provided. It appears that at least a part of the population used a rather low dose (mean 2.4 g daily) and might not have received full dose to treat a relapse (*i.e.* up to 5 g daily). Therefore it is unknown which part of the population included could be defined as failing 5-ASA.

The results of the primary and major secondary endpoints based on the ITT population are shown in Table 3. Both studies showed a statistically significant difference in the proportion of patients achieving clinical remission. The overall difference in clinical remission rates between Cortiment 9 mg and placebo was statistically significant; mean difference was 10.4% (95% CI: 2.2-18.7) and 12.9% (95% CI: 4.6-21.3) in study CB-01-02/01 and CB-01-02/02, respectively. Although there was a trend for higher rates of clinical and endoscopic improvement with Cortiment 9 mg, no statistically significant differences were observed with placebo (observed differences were ≤ 10%). A lower dose of Cortiment 6 mg was not effective at all.
No comparisons were made between Cortiment 9 mg and the active comparators. Exploratory analysis versus placebo did not show statistical significance for Asacol and borderline significance for Entocort; mean difference in clinical remission rates were 5% (95% CI: -2.7 – 12.1) and 8.1% (95% CI: 0.4-15.9%), respectively.

Table 3. Summary of the main clinical efficacy endpoints (ITT population – worst case scenario).

	Study CB-01-02/01				**Study CB-01-02/02**			
ITT population	**Placebo N=121**	**Cortiment 9 mg N=123**	**Cortiment 6 mg N=121**	**Asacol[†] N=124**	**Placebo N=89**	**Cortiment 9 mg N=109**	**Cortiment 6 mg N=109**	**Entocort[†] N=103**
Primary endpoint								
Remission rate (95% CI)	7.4% (2.8, 12.1)	17.9% (11.1, 24.7)	13.2% (7.2, 19.3)	12.1% (6.4, 17.8)	4.5% (0.2, 8.8)	17.4% (10.3, 24.6)	8.3% (3.1, 13.4)	12.6% (6.2, 19.0)
Mean difference with placebo (95% CI)		10.4%* (2.2, 18.7)	5.8% (-1.8, 13.4)	4.7% (-2.7, 12.1)		12.9%* (4.6, 21.3)	3.8% (-3.0, 10.5)	8.1%[$] (0.4, 15.9)
Major secondary endpoints								
Clinical improvement rate (95% CI)	24.8% (17.1, 32.5)	33.3% (25.0, 41.7)	30.8% (22.4, 38.8)	33.9% (25.5, 42.2)	33.7% (23.9, 43.5)	42.2% (32.9, 51.5)	25.7% (17.5, 33.9)	33.0% (23.9, 42.1)
Mean difference with placebo (95% CI)	-	8.5% (-2.8, 19.9)	5.8% (-5.5, 17.0)	9.1% (-2.3, 20.4)	-	8.5% (-5.0, 22.0)	-8.0% (-20.8, 4.8)	-0.7% (-14.1, 12.7)
Endoscopic improvement rate (95% CI)	33.1% (24.7, 41.4)	41.5% (32.8, 50.2)	35.5% (27.0, 44.1)	33.1% (24.8, 41.3)	31.5% (21.8, 41.1)	42.2% (32.9, 51.5)	25.7% (17.5, 33.9)	36.9% (27.6, 42.2)
Mean	-	8.5%[#]	2.5%[#]	0.0%	-	10.7%[#]	-5.8%[#]	5.4%

difference with placebo (95% CI)				(-11.8, 11.8)				(-8.0, 18.8)

CI: Confidence interval; * p<0.025; $ p<0.05; # A statistical comparison of the rates of mucosal improvement in the Cortiment 9 mg and 6 mg groups vs. placebo were not conducted as no significant different from placebo with respect to clinical improvement was observed (hierarchical order testing); † not powered to show statistical significance versus Cortiment.

The number of patients with treatment failure appeared comparable between Cortiment 9 mg and placebo. *Post-hoc* analyses stratified for extent of disease and disease severity showed that remission rates were lower for patients with extensive disease and moderate disease severity, which might be expected. Data suggest that at least for study CB-01-02/01 results were not statistically significant for patients with extensive colitis and moderate disease severity. Further *post-hoc* analyses to assess the benefit in patients with mild disease severity showed inconsistent results between studies and between primary and secondary endpoints. This may partly be explained by the limited number of patients with mild disease severity.

Because of the observed lack of efficacy of Asacol the MEB requested a post-hoc analysis on the primary efficacy endpoint stratified for use of 5-ASA treatment at screening including a discussion of potential differences.
These data showed that remission rates appeared comparable for patients with or without 5-ASA at screening for study CB-01-02/01 (Table 4). Only placebo rates appeared somewhat lower in patients who did not use 5-ASA before. For study CB-01-02/02, remission rates were higher for Cortiment 9 mg, but appeared lower for all other treatment groups in patients not on 5-ASA compared to patients already on 5-ASA. This is especially true for Entocort. According to the MAH this might be a carry-over effect of the prior 5-ASA use. Although some carry-over effect cannot be excluded, it is not likely that this can entirely explain the relatively large effect of Entocort in patients using 5-ASA at screening. If a substantial carry-over effect would exist, this would also impact the results of the other treatment groups, whereas for instance placebo rates were much lower.

Table 4. Remission rates (primary efficacy outcome) stratified for prior 5-ASA use – *Post hoc* analyses

	Patients not on 5-ASA		**Patients on 5-ASA**	
Treatment	**Remission n/N (%)**	**Difference vs. placebo (95% CI)**	**Remission n/N (%)**	**Difference vs. placebo (95% CI)**
Study CB-01-02/01				
Cortiment 9 mg	10/59 (17.0%)	12.5% (1.2%, 23.8%)	12/64 (18.8%)	9.4% (-2.2%, 21.0%)
Cortiment 6 mg	6/42 (14.3%)	9.8% (-2.3%, 22.0%)	10/79 (12.7%)	3.3% (-6.5%, 13.2%)
Asacol	7/52 (13.5%)	9.0% (-2.0%, 20.1%)	8/72 (11.1%)	1.8% (-8.0%, 11.6%)
Placebo	2/45 (4.4%)	-	7/75 (9.3%)	-
Study CB-01-02/02				
Cortiment 9 mg	9/39 (23.1%)	23.1% (9.9%, 36.3%)	10/70 (14.3%)	7.6% (-2.7%, 18.0%)
Cortiment 6 mg	2/37 (5.4%)	5.4% (-1.9%, 12.7%)	7/72 (9.7%)	3.1% (-6.3%, 12.4%)
Entocort	1/31 (3.2%)	3.2% (-3.0%, 9.5%)	12/72 (16.7%)	10% (-0.7%, 20.7%)
Placebo	0/29 (0%)	-	4/60 (6.7%)	-

The RMS considered that the interpretation of the results of the *post-hoc* analyses in terms of clinically relevant efficacy is highly dependent on the placebo rates, which differ between the studies. The number of patients reaching remission on placebo is very low to zero. This means that the addition of only a few patients might render different results, which makes the interpretation less reliable. Overall, the results of the *post-hoc* stratified analysis do not provide compelling and consistent differences in remission rates for Cortiment 9 mg in patients with or without prior 5-ASA use. Further, interpretation of post-hoc analyses is hampered by inherent deficiencies like loss of randomisation and control of type 1 error.

Remission rates were higher for patients in India (study CB-01-02/01) and Eastern Europe (study CB 01-02/02). However, this was shown for both Cortiment and placebo groups. The exact reasons are unknown, but might be related to for instance differences in standards of care. However, results

should be interpreted carefully as numbers were low especially for placebo. Stratified analyses showed that the absolute difference between Cortiment and placebo appeared consistent between geographical regions. Regarding the main secondary outcomes, differences between geographic regions are less obvious or negligible. No data were available on the response of the active comparators.

Quality of clinical studies, compliance with GCP
The MAH states that all clinical studies were conducted in accordance with GCP as described in the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constituted compliance with the ethical principles described in the Declaration of Helsinki.

During blinded data review of phase III study CB-01-02/02, prior to database lock, it was observed that some sites were outliers with regards to patient recruitment, histological assessment and response rates. Additional audits were conducted by a clinical research company to assess the quality and validity of the study data. As a result of these audits, all data from the ITT population of four sites were excluded from the ITT efficacy data; patients remained eligible for the safety set. This was decided prior to database un-blinding due to GCP violations noted during audits.
Overall trial management and monitoring by the MAH were sufficient and GCP issues are considered sufficiently addressed.

V.4 Clinical safety

The overall number of patients using the recommended dose of Cortiment 9 mg is about 300 patients, which is acceptable given the well-known safety profile of orally administered budesonide in inflammatory bowel diseases at a comparable dose and duration of use. Maximum treatment duration was 8 weeks and no long-term data are available. This is acceptable as the MAH only applied for treatment of induction of remission and does not include maintenance of remission.

The vast majority of safety data is retrieved from the phase III clinical efficacy and safety studies (CB-01-02/01 and CB-01-02/02). The incidence of TEAEs and related TEAEs was similar across all treatment groups and appeared comparable between studies. Most frequently occurring treatment-emergent AEs occurred in the system organ class (SOC) gastrointestinal disorders and most frequently reported preferred terms were ulcerative colitis (i.e. worsening of underlying condition) and headache. These were also the most frequently reported related TEAE. Only headache appeared to occur more frequently in the Cortiment groups compared to other treatment groups. All other related TEAEs occurred infrequently (< 2% of all patients), except for decreased blood cortisol levels. The observed decrease in plasma morning cortisol did not appear to be translated into an increase in clinical glucocorticoid effects. In the Phase 2 study CRO-03-53 the effect of Cortiment 9 mg on the hypothalamus-pituatary-adrenal (HPA) axis was specifically evaluated through a short Synacthen test performed at the end of 8 weeks of treatment: no evidence of negative effects on HPA was detected. Overall, only slight changes in potential glucocorticoid-related effects were seen for the budesonide treatment groups, which confirm the better safety profile compared to systemic steroids. No new safety signals were identified.

In conclusion, the data confirm the known favorable safety profile for oral budesonide. The current product information adequately reflects the present knowledge and experience with oral budesonide formulations.

V.5 Risk Management Plan

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

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

Safety Concern	**Proposed Risk Minimisation Measures (routine and additional)**	**Proposed risk minimisation activities (routine)**

Safety Concern	Proposed Risk Minimisation Measures (routine and additional)	Proposed risk minimisation activities (routine)
Important Identified Risks		
Potential relapse of Ulcerative Colitis	Routine PV	SmPC section 4.8
Important potential risks		
None		
Important Missing Information		
Use in pregnancy/lactation	Routine PV	SmPC section 4.6
Paediatric studies/off-label use in children	Routine PV	SmPC section 4.2
Use in co-morbid conditions e.g., hepatic and renal insufficiency	Routine PV	SmPC section 4.2
Off-label use	Routine PV	SmPC section 4.1
Use in the elderly	Routine PV	SmpC section 4.2

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

V.6 Discussion on the clinical aspects

V.6.1 Benefit-Risk assessment during decentralized procedure

The proposed indication for oral Cortiment 9 mg is induction of remission in patients with mild to moderate active ulcerative colitis. Currently available oral formulations of budesonide are not recommended for treating distal colonic lesions such as those seen in UC due to extensive absorption from the small intestine and right ascending colon whereas rectal formulations are only indicated for patients with UC limited to the recto-sigmoid junction.

Pharmacokinetic studies indicate that budesonide given as Cortiment (MMX formulation) is released mainly in the colon, which is a preference to treat proximal and distal UC. Furthermore, data indicate slower release of budesonide from the MMX formulation compared to current oral formulations (Entocort).

The two pivotal phase III studies (CB-01-02/01 and CB-01-02/02) with a similar design included adult patients with active UC of mild to moderate severity (4≤UCDAI≤10) and confirmed by histology; patients with limited distal proctitis were excluded. Two dose groups of budesonide MMX (6 mg and 9 mg) were studied versus placebo. The highest dose of 9 mg is similar to the recommended daily dose of currently available formulations of budesonide used in the treatment of inflammatory bowel disease (M Crohn). Both studies included an additional reference arm; Asacol 2.4 g daily (study CB-01-02/01, performed predominantly in the US and India) and Entocort 9 mg (study CB-01-02/02, performed predominantly in the EU).

A statistically significant difference in the proportion of patients achieving clinical remission (recommended clinical endpoint) at week 8 was shown for Cortiment 9 mg versus placebo (17.9% versus 7.4% and 17.4% versus 4.5% in study CB-01-02/01 and CB-01-02/02, respectively). The clinical relevance of the observed effect of Cortiment 9 mg could be, however, questioned as the effect size is limited (10%-13% difference compared to placebo). Placebo remission rates were low and also lower than expected. This might be (partly) related to the strict definition of remission used including mucosal healing. However, the doubt on clinically relevant efficacy is supported by the lack of a statistical significant effect on the major secondary endpoints clinical and endoscopic improvement rate (observed absolute differences versus placebo were ≤ 10%), which are commonly used within UC trials. It is not known whether a higher dose might be more effective as this was not explored. Post-hoc analyses stratified for extent of disease and disease severity showed that remission rates were lower for patients with extensive disease and moderate disease severity, which might be expected. The data suggest that at least for study CB-01-02/01 results were not statistically significant for

patients with extensive colitis and moderate disease severity. The RMS therefore questioned whether the robustness of efficacy is shown. This is especially of importance in a patient population that may present itself with a range in disease severity and disease extent.

Active comparators were included for validation purposes, of which the results of Asacol are of most importance, as this is considered a well-established first-line treatment in patients with UC. However, the data (study CB-01-02/01) did not show a statistically significant efficacy of Asacol over placebo based on primary and major secondary endpoints. The validity of the data for the target population is therefore questioned.

Post-hoc analysis stratified for prior 5-ASA use did not provide compelling and consistent differences in remission rates for Cortiment 9 mg in patients with or without prior 5-ASA use.

The use of Entocort as active comparator is questioned because of the site of release of active substance. Moreover, it is not recommended in clinical practice. Instead, systemic corticosteroids are widely used as second line treatment. Although direct comparisons with literature data are hampered by differences in populations included and efficacy criteria used, remission rates up to 50% have been reported for systemic corticosteroids (up to 50%), which are far higher than those reported for Cortiment.

The safety profile is in line with other budesonide formulations used for inflammatory bowel disease and confirms the better safety profile compared to systemic corticosteroids.

V.6.2 Benefit-risk assessment

The anti-inflammatory effect of budesonide is well known; it is used in rectal formulations for the treatment of proctitis, generally in addition to treatment with 5-ASA. Although the absolute effect was limited, the primary endpoint was met in both studies. Statistically significant superiority in induction of remission was demonstrated over placebo.
The RMS considered that treatment with Cortiment can be beneficial for some patients. Given the limitations of the currently available treatments, Cortiment may present physicians with an additional therapeutic option. In particular, there is a role for Cortiment in the treatment of colitis ulcerosa, if used to induce remission before treatment with systemic corticosteroids is initiated, which is associated with more severe adverse events.
Based on the provided data the majority of CMSs agreed with the assessment and conclusions of the RMS. Notwithstanding this agreement, concerns regarding the proposed indication of Cortiment were raised by some CMSs. A second line indication in patients not eligible to 5-ASA was proposed.
Further additional information on the benefit/risk of Cortiment as compared to the medicinal products form the well-established treatment model for UC had to be submitted.

The MAH provided sufficient additional data to substantiate the fact that current treatment is often not sufficiently effective. It is reported that in mild/moderate disease mesalazine has response rates between 40%-70% and remission rates of 15%-20%. The limitations of current treatment are acknowledged. Furthermore, the applicant refers to the CONSORT statement to support the use of Odds Ratios as a tool to compare different trials when the primary outcome is binary2. In this respect, the ORs versus placebo in studies CB-01-02/01 and CB-01-02/02 of 2.7 and 4.5 were higher as compared to other treatments for mild to moderate UC. Also, preliminary data from a phase 3b study was submitted. This was a multi-center, randomized, double blind, parallel group, 12-months extended use study comparing budesonide MMX 6 mg and placebo in patients with mild to moderate UC who achieved both clinical and endoscopic remission after two phase 3 studies or an Open Label study with budesonide MMX 9 mg. The safety analysis included 123 patients (n=62 for budesonide MMX 6 mg, n=61 for placebo). The 12-month safety data did not reveal new safety issues. It should be noted, that these were preliminary data and the number of patients exposed to budesonide MMX 6 mg (n=62) was small.

The opinion of some international clinical experts in the field of inflammatory bowel disease was presented in the dossier.
The experts expressed the opinion that there is a high unmet medical need for new treatments in UC, as currently available treatments are not sufficiently effective in all individuals. In a considerable number of patients, the first step of 5-ASA is not effective enough. According to the various

international guidelines, corticosteroids are then the key treatment for the majority of patients not responding to 5-ASA, but the side effects of systemic corticosteroids are a significant issue. Due to these side effects compliance is reduced and long term adverse effects (for example osteoporosis, diabetes) result in a treatment at the lowest dose for the shortest possible duration. In the opinion of the experts, a steroid administered in a more local way and which is not associated with the many systemic side effects of systemic corticosteroids (mostly prednisolone), satisfy a medical need.
Furthermore, the experts indicated that the small effect size in the phase 3 studies was due to the study design and strict criteria of including only patients with active disease as confirmed by biopsy and the strict criteria of clinical remission including endoscopy. Other UC studies in the past have used less strict criteria and as such the rates for placebo and the investigational drug were higher in past studies.
The experts considered the results of the phase 3 studies to be of clinical relevance, in the light of the unmet medical need and the balance between risk and benefit, as the risk of side-effects of locally administered budesonide was very low (no difference from placebo) and the drug was more effective than placebo.
The fact that the Asacol arm in study C-01-02/01 was not effective did not surprise the experts, as this confirms the fact the currently available treatment is not sufficiently effective in many patients and there is an unmet medical need for new treatment options. Based upon their clinical experience, the experts do not consider under-treatment or the risk of under-treatment doing harm to patients to be an issue. Patients not sufficiently responding to corticosteroids (local or systemic) will be treated with more effective treatment options (unfortunately with a worse safety profile). Current guidelines advise TNF-α inhibitors in such situations.

The MAH did not consider it necessary to restrict the indication to a second line indication based on the comments raised and maintained the initially proposed indication. It was reinforced that within the studies Cortiment provided a benefit in treatment naïve patients as well as in 5-ASA treatment failures with active disease. This has been shown for each study separately (see also Table 3 Overview of studies). Although it is acknowledged that the studies submitted do not allow for a first line treatment a second line treatment is not evident either. The MAH then presented a post-hoc analysis based on the pooled data of the two studies. This analysis shows that in both patient groups (5-ASA naïve as well as 5-ASA treatment failures) Cortiment 9 mg is more effective than placebo for the primary endpoint. Further, the MAH shows that ORs for Cortiment are in the same range as that for other main treatments of UC. However, interpretation of results across studies is limited by differences in study design.
The RMS was of the opinion that the apparent lower remission rates in patients with moderate disease severity and extensive disease might be expected given the more difficult to treat population. Post-hoc analysis using a different (less stringent) classification of moderate disease showed somewhat higher remission rates for the pooled data (14.1% versus 9.5% and 11.3% for the individual studies using the per protocol definition), which can be expected. Nevertheless, the RMS is of the opinion that the results of the post-hoc analyses should be interpreted carefully due to lack of statistical power and no firm conclusions can be drawn from these analyses.
The RMS concluded that this 9 mg prolonged-release formulation of budesonide may present physicians a new therapeutic option for patients with mild to moderate ulcerative colitis. Taking into account the known (historical and demonstrated combined) efficacy of budesonide in the treatment of UC combined with the – for corticosteroids – very mild adverse events profile, the RMS agrees with the MAH that the overall data (i.e. submitted studies, general literature and expert opinions) support the use of Cortiment for the induction of remission in both mild and moderate UC. The more general indication as proposed by the MAH was therefore acceptable as it does not claim the treatment as either first or second line. Section 5.1 of the SmPC was further adapted to adequately reflect the results of the studies submitted. This allows the prescriber and patient to make a well informed choice.
Although the positive benefit-risk balance for Cortiment was generally agreed upon, agreement on whether a first or second line indication is more suitable was not reached. Therefore a CMDh referral was requested by one of the Concerned Member States.

CMD(h) Referral

Referral grounds
The procedure was referred to the CMDh due to a different point of view between RMS and one CMS, regarding the submitted data for the claimed first-line indication.

This CMS considered that based on the data submitted only a restricted indication in patients not eligible to 5-ASA, could be accepted. The MAH was requested to justify why the data provided should be considered sufficient for a first line indication.

Outcome
Recognizing that according to current Guidelines, placebo-controlled studies may not support a first line indication in moderate to severe ulcerative colitis disease and that 5-ASA remains the standard of care, the MAH agreed to restrict the indication to patients where the 5-ASA treatment is not sufficient. The procedure was finalized with approval of this restricted indication and addition of information that some patients may benefit from treatment initially with Cortiment in section 5.1 of the SmPC.

VI. USER CONSULTATION

The package leaflet (PIL) has been evaluated via a pilot user consultation study with 4 participants, all considered to be potential users of the tablets (above 18 years). Inclusion and exclusion criteria and demographics (gender, age and educational distribution) are acceptable.
A questionnaire with open questions was developed with the aim of collecting preliminary feedback for finalising the PL text and questionnaire, before the subsequent main test. The pilot stage of testing illustrated that overall, the Cortiment PL was clear, legible and user friendly. Points of improvement were raised and changes were introduced to the PL in order to ensure sufficient communication and readability of all key aspects.
The two main test rounds were conducted with cohorts of 10 participants. The results of both rounds showed that the PL meets the EU Guideline success criteria defined as 90% of the subjects being able to find the information within the PL, with 90% of these subjects being able to demonstrate that they understand this information. In conclusion, the readability test has been sufficiently performed.

VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cortiment 9 mg, prolonged-release tablets has a proven chemical-pharmaceutical quality and is an approvable hybrid form of Entocort 3 mg capsules. Entocort is a well-known medicinal product with an established favourable efficacy and safety profile.

The Medicines Evaluation Board of the Netherlands came to a positive decision during the national assessment of Cortiment. The MEB took into consideration that the anti-inflammatory effect of budesonide is well known. Even though the absolute effect size is limited, the primary endpoint was met in both pivotal studies. Statistically significant superiority in induction of remission was demonstrated over placebo.
The safety profile of Cortiment is considered comparable to that known for locally acting corticosteroids.
In view of all data, the MEB considers that treatment with Cortiment can be beneficial for some patients and may present physicians with an additional therapeutic option. A national marketing authorisation for Cortiment 9 mg, prolonged-release tablets was granted in the Netherlands on 28 February 2013.

Based on this national marketing authorisation the MAH submitted an application to several MSs via the MRP procedure. The MAH provided sufficient additional data to demonstrate that current treatment is often not sufficiently effective. This was substantiated with relevant expert opinions. Agreement between the member states was however not reached during the 90 days mutual recognition procedure. One of the CMSs started a referral.
Based on the raised comments regarding the indication, the MAH proposed to restrict the indication as follows:
The product is indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient.

In the Board meeting of 2 October 2014 the MEB supported this indication. Based on the response received and some further amendments in sections 4.1 and 5.1 of the SmPC, consensus was reached between the RMS and CMSs. The referral was finalised with a positive outcome on 17 October 2014.

The following post-approval commitments were made:

- A full ERA will be submitted. This commitment was partially fulfilled with variation NL/H/3168/001/II/001, however further commitments were made in order to fully comply to the ERA requirements.

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
Addition of an active substance manufacturer which uses a CEP; extension or introduction of a re-test period/storage period.	NL/H/3168/IB/002/G	Type IB grouped variation	5 February 2015	7 March 2015	Approval	N
Update of the ERA	NL/H/3168/001/II/001	Type II variation	13 January 2015	22 July 2015	Approval	N