This module reflects the scientific discussion for the approval of Mesalazine Nordic 1 g, 2 g and 4 g, granules for rectal suspension. The procedure was finalised on 21 January 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.

A list of literature references is given on page 11.
### List of abbreviations

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<tr>
<td>ASA</td>
<td>Aminosalicyc acid</td>
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<td>5-ASA</td>
<td>5-Aminosalicyc acid, Mesalazine</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines and HealthCare</td>
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<td>ECCO</td>
<td>European Crohn's and Colitis Organisation</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ESPGHAN</td>
<td>European Society for Paediatric Gastroenterology Hepatology and Nutrition</td>
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<td>FDA</td>
<td>Food and Drug Administration of the United States</td>
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<td>IL</td>
<td>Interleukine</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board of the Netherlands</td>
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<td>NSAID</td>
<td>Non-steroidal Anti-inflammatory Drug</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package leaflet</td>
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<td>POR</td>
<td>Pooled Odds Ratio</td>
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<td>PPAR</td>
<td>Peroxisome Proliferator Activated Receptor</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<td>SmPC</td>
<td>Summary of product characteristics</td>
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<td>TNF</td>
<td>Tumour necrosis factor</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>UC</td>
<td>Ulcerative Colitis</td>
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I. **INTRODUCTION**

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mesalazine Nordic 1 g, 2 g and 4 g, granules for rectal suspension from Nordic Group BV.

The product is indicated for the treatment of mild to moderate left-sided ulcerative colitis (UC). A comprehensive description of the indications and posology is given in the SmPC.

Mesalazine is used for the treatment of UC because of its anti-inflammatory properties. The exact anti-inflammatory action of mesalazine is unclear, but it appears to act topically on the damaged epithelium cells of the intestine rather than systemically.

This decentralised procedure concerns a bibliographic application in accordance with Article 10a of Directive 2001/83/EC, relating to applications relying on well established medicinal use supported by publicly available literature. As such, the application only contains literature data and no additional non-clinical, clinical, pharmacological or toxicological studies have been conducted in animals or humans for the product Mesalazine Nordic granules for rectal suspension.

Mesalazine tablets and enemas for the treatment of ulcerative colitis have been authorized for marketing for more than 10 years in many countries worldwide. Mesalazine is available as oral formulations as well as formulations for rectal application. Pentasa rectal suspension (NL License RVG 11782) and Salofalk enema (NL License RVG 15393) have been registered in the Netherlands since 1987 and 1991, respectively. A third mesalazine enema, Asacol, was authorised in the Netherlands in 1993, but is no longer registered. Mesalazine suppositories are also registered.

The concerned member states (CMS) involved in this procedure were Denmark and the United Kingdom.

II. **QUALITY ASPECTS**

II.1 **Introduction**

Mesalazine Nordic is formulated as almost white to light grey to light pink or pale brown granules.

The granules are packed in an aluminium foil sachet. One sachet contains either 1 or 2 g of mesalazine. Mesalazine Nordic 4 g granules is divided equally into 2 sachets containing 2 g of active substance each.

The product is supplied with polyethylene enema bottles fitted with a tip and valve for rectal enema preparation and application.

The excipients are: xanthan gum, crosscarmellose sodium, sodium chloride.

II.2 **Drug Substance**

The active substance mesalazine is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is very slightly soluble in water and practically insoluble in ethanol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

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 MAH applies the requirements laid down in the Ph.Eur. monograph for mesalazine and additional requirements for particle size. The control tests and specifications for drug substance are adequately drawn up. Batch analysis certificates have been provided for two batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described in detail and the choice of excipients is adequately justified. Formulation and manufacturing trials have been performed. The objective of the development process was to develop a formulation (enema) which could be easily dispersed after reconstitution having required suitable viscosity similar to the ready-made enemas on the market. The MAH set the target pH value at 4.0 – 5.0 as in general a pH value between 4.0 – 10.0 is acceptable for rectal preparations. pH values outside this range may cause irritation of the rectal mucosa. The toxicity of the product was also properly justified. The MAH demonstrated that volume and viscosity of the Mesalazine Nordic formulation are within range of the approved mesalazine enemas Pentasa, Asacol and Salofalk. Literature data confirm that enemas with similar volume and viscosity spread to the splenic flexure thereby reaching the area affected in left-sided, i.e. distal, ulcerative colitis. The MAH provided dissolution data, showing fast dissolution of Mesalazine Nordic. Considering that the proposed particle size limit is in line with the particle size of the reference products, the fast dissolution (>80% in 5 minutes), and the clinical justification as presented in section IV, comparative dissolution data versus the other mesalazin enemas can be provided post approval. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The active substance and excipients are separately sifted and then mixed. The powder mixture is granulated using purified water. The granulate is then dried, sifted to obtain the required particle size, blended and then filled into Alu-Alu stick packs. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 2 batches of the 1 g strength and 2 batches of the 4 g strength.

Control of excipients
The excipients comply with the Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, pH of the reconstituted product, viscosity of the reconstituted product, uniformity of dosage units, assay, related substances, dispersibility and microbiological quality. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two batches of the 1 g and 4 g strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on 2 batches of the 1 g strength, 2 batches of the 4 g strength, and one development batch of the 2 g product stored at 30°C/70% RH (6-12 months, long term) and 40°/75% RH (6 months). The conditions used in the stability studies are not according to the ICH stability guideline, however, this is acceptable as the long-term storage condition is comparable to climate zone IV (worst case). The batches were stored in the intended sachets. The stability results do not show specific trends, however, out-of-specification results are noted for assay. They are sufficiently discussed. Based on the available stability data, a shelf-life of 15 months has been
In view of the photosensitivity of mesalazine, the product should be stored in the original package for protection against light. The product has to be used immediately after preparation.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mesalazine Nordic has 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 complete process validation at full production scale. Process validation will be performed one further 1 g batch and one further 4 g batch.
- The MAH committed to provide the data regarding the comparative dissolution testing versus the other mesalazine enemas (as per FDA guidance) together with a discussion of the observed profiles, within 3 months after approval of the procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Mesalazine Nordic is intended for substitution of comparable products on the market, 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

The pharmacological, pharmacokinetic and toxicological properties of mesalazine are well known, including those specific for the current route of administration as similar products are already on the 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 for this well-established medicinal product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mesalazine 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. Mesalazine enemas qualify as well-established medicinal products.

IV.2 Pharmacokinetics

The MAH described the pharmacokinetics in general. Pharmacokinetics of mesalazine are well known, after oral as well as after rectal application. The description in section 5.2 of the SmPC is also very general, and is in line with the SmPCs of Asacol, Pentasa and Salofalk, which are indicated, besides other parts of the colon, for treatment of left-sided ulcerative colitis.
The Mesalazine Nordic liquid enema is qualitatively and quantitatively different, which results in a different pH of the liquid, a different viscosity and a different tonicity. Overall, the formulation characteristics are in the range of Salofalk, Asacol and Pentasa. These three formulations have their own specific release and absorption characteristics, resulting in efficacy and safety properties which are product specific. As Mesalazine Nordic is not identical or similar to one of these formulations, this may result in specific release and absorption characteristics.

The MAH provided sufficient data to support that distribution, retention and absorption of the Mesalazine Nordic enema will be within the range of Salofalk, Asacol and Pentasa. These three formulations have their own specific release and absorption characteristics, resulting in efficacy and safety properties which are product specific. As Mesalazine Nordic is not identical or similar to one of these formulations, this may result in specific release and absorption characteristics.

Moreover, mesalazine will be absorbed partly as the inactive N-Ac-5-ASA due to metabolism in the colon by bacteria or due to metabolism by the liver. It is not expected that metabolism in the colon by bacteria will be affected by the difference in tonicity. The effect on absorption of intact mesalazine is not clear, but not expected to differ to a great extent (if even different) compared to Salofalk, Pentasa and Asacol. In addition, its local availability is considered in the same range. Literature data indicate that there is no evidence of dose-related adverse events between 1-4 g mesalazine for rectal enemas (Hannauer et al. 1998) or after oral administration (4.8 g versus 2.4 g, Hannauer et al. 2007).

Therefore, although it can not be excluded that absorption might be somewhat higher, or lower, for the current product compared to reference products, this is not likely to be of clinical relevance in terms of safety.

IV.3 Pharmacodynamics

The exact anti-inflammatory action of mesalazine in UC is unclear, but it appears to act topically on the damaged epithelium cells of the intestine rather than systemically. Prostaglandins, interleukines (e.g. IL-2) among other factors are involved. By binding to peroxisome proliferator activated receptor (PPAR)-γ, a transcription factor that modulates the inflammatory response of monocytes and macrophages, the production of nitric oxide and macrophage-derived cytokines, such as TNF-α, IL-1 and IL-6 may be inhibited (Rousseaux et al., 2005).

Though the exact mechanism of action of mesalazine is unclear, the MAH described sufficiently what is currently known about the mechanism of action. Mesalazine is a well-known active substance with a long-term and well-established use in the treatment of UC.

IV.4 Clinical efficacy

The MAH submitted bibliographic data about the efficacy and safety of mesalazine from the period 1966 until 2013, including two Cochrane reviews. This is considered acceptable provided that the these bibliographic efficacy and safety data are applicable to Mesalazine Nordic.

The overview of clinical efficacy of rectal mesalazine treatment for left-sided ulcerative colitis is split up into two sections, largely based on the results of two Cochrane reviews:

1) induction of remission (Marshall et al. 2010)

Induction of remission of left-sided colitis ulcerosa with mesalazine

With respect to the induction of remission of UC with mesalazine, the MAH exclusively used data from a Cochrane review of 2010 (Marshall et al. 2010). Eligible trials enrolled patients with a distal disease margin less than 60 cm from the anal verge or distal to the splenic flexure, as determined by either barium enema or colonoscopy.

In the 38 studies that satisfied the inclusion criteria the total daily dose of rectal mesalazine ranged from 1 g to 4 g and the duration of follow up ranged from two to eight weeks. In 28 of the studies mesalazine was delivered as liquid or gel enema, 7 studies included a foam enema, and suppositories were used in 7 studies.

Rectal mesalazine treatment was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission. Percentages of patients with disease improvement or in remission in the mesalazine treatment arms ranged between 42%-85% compared to 13%-41% for the
placebo treatment arm. The pooled odds ratio (POR) for symptomatic remission was 8.30 (8 trials, P < 0.00001).

Symptomatic remission of rectal mesalazine treatment was found to be more effective than placebo treatment for different mesalazine doses (>0–4 gram) in the Cochrane review. Symptomatic remission of 1 versus 2 grams and 2 versus 4 grams mesalazine were similar (POR 1.09 (95% CI 0.58-2.06) vs. 1.43 (95% CI 0.50-4.13) respectively).

No consistent difference in efficacy was noted among the various rectal mesalazine formulations (liquid enema, foam enema or suppository) in the Cochrane meta-analysis (2010).

Maintenance of remission of left-sided colitis ulcerosa with mesalazine
In the Cochrane analyses (Marshall 2012), rectal mesalazine was significantly superior to placebo for maintaining symptomatic remission over a period of 12 months. Sixty-two per cent of patients in the rectal mesalazine group maintained symptomatic remission compared to 30% of patients in the placebo group (4 studies; 301 patients; 95% CI 1.26 to 3.90).

In the included studies, 0.5 to 4 gram mesalazine was administered a day. In 5 out of 9 included studies, mesalazine was administered once daily. There was no evidence for a dose response relationship. No differences were observed with respect to the type of formulation. Optimal duration of maintenance therapy after successful induction of remission remains unclear.

Using data from two recent Cochrane reviews (Marshall 2010 and 2012), the MAH has provided a good overview about the general efficacy of rectal mesalazine treatment for UC. The indication of left-sided mild to moderate UC falls within the scope of this Cochrane review. The results of the Cochrane review are therefore applicable to the current application. The study results of studies included in the Cochrane review show that rectal mesalazine is superior to placebo for inducing symptomatic improvement and remission of UC. This also holds for maintaining remission.

IV.5 Clinical safety

The safety profile of mesalazine is well-known. Commonly reported adverse events during mesalazine treatment in medical literature include rectal disorder (e.g. haemorrhoids, anal fissure, and anal irritation), abdominal pain and diarrhea.

The following serious adverse events have been rarely reported: blood dyscrasias, nephritis, pancreatitis, hepatitis, exacerbation of UC, cardiovascular toxicity, and pneumonia.

Six cases of fatal blood dyscrasias and one case of fatal myocarditis have been reported in literature.

Overdose
No cases of overdose with mesalazine enemas have been reported.

Paediatric population
Joint ECCO and ESPGHAN evidence-based consensus guidelines (2012) recommend rectal mesalazine treatment in children. No dose recommendation for children has been formulated.

Impaired liver and/or renal function
In patients with impaired liver and kidney functions, possible decrease in the rate of elimination and increased systemic concentration of mesalazine may constitute an increased risk of nephrotoxic or hepatotoxic adverse reactions.

Patients with impaired renal and/or liver function are more prone to experience adverse events of mesalazine treatment. This important information is described in a separate subsection of SmPC section 4.4.

Drug-drug interactions
The concurrent use of mesalazine with other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions.
Concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving azathioprine or 6-mercaptopurine.

The clinical overview presented by the MAH sufficiently describes the safety profile of general mesalazine treatment based on currently available literature data.

**IV.6 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 Mesalazine Nordic.

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<td>Important identified risks</td>
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<td>Kidney function disorders</td>
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<td>Important potential risks</td>
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

**IV.7 Discussion on the clinical aspects**

Well established use is adequately demonstrated for mesalazine rectal formulations. No new clinical studies were conducted. The MAH justified that the efficacy and safety data obtained with other, comparable medicinal products apply to Mesalazine Nordic as well. Risk management is adequately addressed.

**V. USER CONSULTATION**

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. A total of 22 participants were questioned about the leaflet in one preliminary test round (two participants) and two consecutive rounds (10 in each testing round).

Thirteen questions were asked, sufficiently addressing the key safety issues. In addition, the participants were asked for an overall impression of the leaflet - what is good and what is bad about the leaflet, lay out and design, overall rating of the leaflet.

Results of both rounds of testing were good. For each question, 100% of participants were able to find the correct information, and all of them were able to answer the questions correctly. Overall, participants were positive about the leaflet and all rated the leaflet either easy or very easy to read. The user testing as conducted by the MAH is acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mesalazine Nordic 1 g, 2 g and 4 g, granules for rectal suspension have a proven chemical-pharmaceutical quality. The MAH demonstrated based on bibliographic data that rectal mesalazine treatment is effective and safe in the treatment of left-sided ulcerative colitis.

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, agreed that the medicinal product can be considered well established with a favourable benefit/risk profile, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 January 2015.
STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Date of end of the procedure</th>
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Literature references


Hanauer SB, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C, Smith-Hall N. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. Can J Gastroenterol. 2007 Dec;21(12):827-34.

