

**PENTASA SLOW RELEASE TABLETS 1G  
(mesalazine)**

**PL 03194/0108**

**UKPAR**

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## LAY SUMMARY

### PENTASA Slow Release Tablets, 1g (mesalazine, slow release tablets, 1 g)

This is a summary of the Public Assessment Report (PAR) for PENTASA Slow Release Tablets 1g (PL 03194/0108). It explains how PENTASA Slow Release Tablets 1g were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use PENTASA Slow Release Tablets 1g.

For practical information about using PENTASA Slow Release Tablets 1g, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What are PENTASA Slow Release Tablets 1g and what are they used for?**

PENTASA Slow Release Tablets 1g contain the active substance, mesalazine, which belongs to a group of medicines known as salicylates. PENTASA Slow Release Tablets 1g are used to treat mild to moderate inflammation of the gut caused by a condition called ulcerative colitis. They can also be used to control ulcerative colitis and prevent it from coming back.

#### **How are PENTASA Slow Release Tablets, 1g used?**

This medicine can only be obtained with a prescription.

PENTASA Slow Release Tablets 1g are taken by mouth. The tablets should be swallowed whole; they should not be crushed or chewed.

The tablets can be dispensed in a small quantity of cold water (approximately 50 ml), stirred and then taken (swallowed) immediately, by patients who have difficulty swallowing the tablets.

To treat an attack of colitis, the doctor will usually prescribe a dose of up to 4g mesalazine, to be taken as four tablets a day in two or three divided doses.

To help prevent further attacks, the doctor will usually prescribe a dose of 2g mesalazine, to be taken as two 1g tablets once a day.

For further information on how PENTASA Slow Release Tablets 1g are used, refer to the package leaflet and Summary of Product Characteristics available on the MHRA website.

#### **How do PENTASA Slow Release Tablets 1g work?**

The tablets release the active ingredient (mesalazine), slowly, which then acts locally to reduce the inflammation and help relieve or stop the pain.

#### **How have PENTASA Slow Release Tablets, 1g s been studied?**

A lower strength of the tablets (500mg) has already been approved for use for the same indications and at the same dosage as this medicine. PENTASA Slow Release Tablets, 1g are considered to be similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Limited, UK) on the basis of *in vitro* comparative dissolution profiles.

The active ingredient, mesalazine, has been used in medicinal products for a long time and the applicant (Ferring Pharmaceuticals Limited, UK) provided data from the published literature on mesalazine.

**What are the benefits of PENTASA Slow Release Tablets, 1g?**

Because this medicine is considered to be similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Limited, UK), its benefits are taken as being the same as those of 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Ltd, UK) in the proposed indications.

**What are the risks associated with PENTASA Slow Release Tablets 1g?**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Because this medicine is considered to be similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Limited, UK), its risks are taken as being the same as those of 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Ltd, UK) in the proposed indications.

For information about side effects that may occur with using PENTASA Slow Release Tablets 1g, please refer to the package leaflet or the Summary of Product Characteristics available on the MHRA website.

**Why are PENTASA Slow Release Tablets 1g approved?**

This medicine is considered to be similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Ltd, UK).

No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of PENTASA Slow Release Tablets 1g outweigh the risks and the grant of the Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of PENTASA Slow Release Tablets 1g?**

The safety information has been included in the Summary of Product Characteristics and the package leaflet for PENTASA Slow Release Tablets 1g, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about PENTASA Slow Release Tablets 1g.**

A Marketing Authorisation was granted in the UK on 02 September 2011.

The full PAR for PENTASA Slow Release Tablets 1g follows this summary.

For more information about treatment with PENTASA Slow Release Tablets 1g, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2014.

**PENTASA SLOW RELEASE TABLETS 1G  
(mesalazine)  
PL 03194/0108**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Ferring Pharmaceuticals Limited a Marketing Authorisation for the medicinal product PENTASA Slow Release Tablets 1g (PL 03194/0108) on 02 September 2011. PENTASA Slow Release Tablets 1g is a prescription-only medicine (POM) indicated in adults, and children from age 15 years or above, for the treatment of mild to moderate exacerbations of ulcerative colitis, and the maintenance of remission from ulcerative colitis.

The is a national, abridged application, submitted under Article 8.3 of Directive 2001/83/EC, as amended, as a line-extension to the existing Marketing Authorisation for Pentasa Slow Release Tablets 500mg (PL 03194/0044), which was authorised to Ferring Pharmaceuticals Limited on 17 December 1992.

The active ingredient, mesalazine, is a bowel-specific aminosalicylate drug that acts locally in the gut and has its predominant actions there, thereby having few systemic side-effects. As a derivative of salicylic acid, mesalazine is also an antioxidant that traps free radicals, which are potentially damaging by-products of metabolism. The mechanism of action of mesalazine is unclear, but may involve inhibition of leucocyte chemotaxis by reducing cytokine formation, reduced free-radical generation and inhibition of the production of inflammatory mediators.

No new non-clinical or clinical data have been submitted, which is acceptable given that mesalazine is a widely used, well-known active substance that has been in clinical use for many years

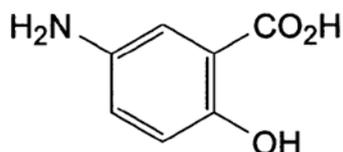
To support this application, the applicant has submitted suitable justification that the criteria for a biowaiver are all met.

No new or unexpected safety concerns arose during review of information provided by the applicant and it was, therefore, judged that the benefits of taking PENTASA Slow Release Tablets 1g outweigh the risks; hence a Marketing Authorisation has been granted.

## PHARMACEUTICAL ASSESSMENT

### ACTIVE SUBSTANCE

INN: Mesalazine  
Chemical Name: 5-amino-2-hydroxybenzoic acid  
Molecular Formula:  $C_7H_7NO_3$   
Structure



Molecular mass: 153.1  
Appearance: An almost white or light grey or light pink powder or crystals, very slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

Mesalazine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance mesalazine are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

### DRUG PRODUCT

#### Other Ingredients

Other ingredients consist of the pharmaceutical excipients povidone, ethylcellulose, magnesium stearate, talc and microcrystalline cellulose. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

#### Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable product containing 1g of mesalazine.

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and Pentasa Slow Release Tablets 500mg.

#### Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

#### Control of Finished Product

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

**Container Closure System**

The tablets are packaged in aluminium blisters. These are packed into cardboard cartons with Patient Information Leaflets in pack sizes of 60 slow-release tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with food.

**Stability**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months has been proposed, with the storage conditions "Do not store above 25°C. Store in the original package."

**Bioequivalence/Bioavailability**

The justification for a biowaiver was considered acceptable, and as a result bioequivalence studies were not required.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPC, PIL and labelling are pharmaceutically satisfactory.

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

**Marketing Authorisation Application (MAA) Form**

The MAA form is pharmaceutically satisfactory.

**Expert Report**

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

## **NON-CLINICAL ASSESSMENT**

### **PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY**

The applicant cross-refers to the non-clinical data for Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Limited UK). As the pharmacodynamic, pharmacokinetic and toxicological properties of mesalazine are well-known, no further non-clinical studies are required and none have been provided.

### **NON-CLINICAL EXPERT REPORT**

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### **ENVIRONMENTAL RISK ASSESSMENT**

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for indications currently treated with Pentasa 500mg prolonged-release tablets, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

### **CONCLUSION**

The grant of a Marketing Authorisation is recommended.

## **CLINICAL ASSESSMENT**

### **CLINICAL PHARMACOLOGY**

The applicant cross-refers to the clinical data for Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Limited, UK). The clinical pharmacology of mesalazine is well-known. No new pharmacodynamic or pharmacokinetic data are provided or required for this application.

### **BIOWAIVER**

The applicant submitted a suitable justification for a biowaiver, in-line with the current guidance. This product is considered essentially similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Ltd, UK) on the basis of *in vitro* comparative dissolution profiles.

### **EFFICACY**

The efficacy of mesalazine is well-known. Efficacy is reviewed in the clinical overview. No new efficacy data have been submitted and none are required for this application.

### **SAFETY**

No new safety data were submitted or required for this application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised from this application.

### **PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

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

### **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**

The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with that for Pentasa 500mg prolonged-release tablets. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in-line with the current guidelines.

### **CLINICAL EXPERT REPORT**

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

### **CONCLUSION**

The grant of a Marketing Authorisation is recommended.

**OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT  
QUALITY**

The important quality characteristics of PENTASA Slow Release Tablets 1g are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of mesalazine are well-known, no additional data were required.

**EFFICACY**

No new data were submitted and none are required for this application. The applicant has submitted suitable justifications to fulfil the biowaiver, in line with current guidelines. This product is considered essentially similar to 2 x Pentasa 500mg prolonged-release tablets (Ferring Pharmaceuticals Ltd, UK) on the basis of *in vitro* comparative dissolution profiles. Efficacy is reviewed in the clinical overview.

**SAFETY**

No new data were submitted and none are required for this type of application. As the safety profile of mesalazine is well-known, no additional data were required. No new or unexpected safety concerns arose during the assessment of this application.

**PRODUCT LITERATURE**

The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for Pentasa500mg prolonged-release tablets. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in-line with the current guidelines.

**BENEFIT/RISK ASSESSMENT**

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

**PENTASA SLOW RELEASE TABLETS 1G  
(mesalazine)**

**(PL 03194/0108)**

**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the Marketing Authorisation application on 07 September 2009.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 11 September 2009.
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 17 December 2009 and 18 May 2011, and the quality dossier on 17 December 2009, 09 September 2010, 16 March 2011, 15 April 2011 and 18 May 2011.
- 4 The applicant responded to the MHRA's request, providing further information on the clinical dossier on 22 July 2010, 20 May 2011, 18 July 2011 and 10 June 2011, and the quality dossier on 22 July 2010, 22 November 2010, 01 April 2011 and 04 May 2011.
- 5 The application was granted on 02 September 2011.

**PENTASA SLOW RELEASE TABLETS 1G  
(mesalazine)****(PL 03194/0108)****STEPS TAKEN AFTER AUTHORISATION – SUMMARY**

The following table lists a non-safety update to the Marketing Authorisation for PENTASA Slow Release Tablets 1g (PL 03194/0108) that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
19 March 2014	Type II	To update section 4.2 (posology) of the Summary of Product Characteristics (SmPC) to include an alternative dosing of once daily, based on the results of a recent clinical trial. As a consequence, the Patient Information Leaflet (PIL) has been updated.	Approved 26 May 2014

**SUMMARY OF PRODUCT CHARACTERISTICS**

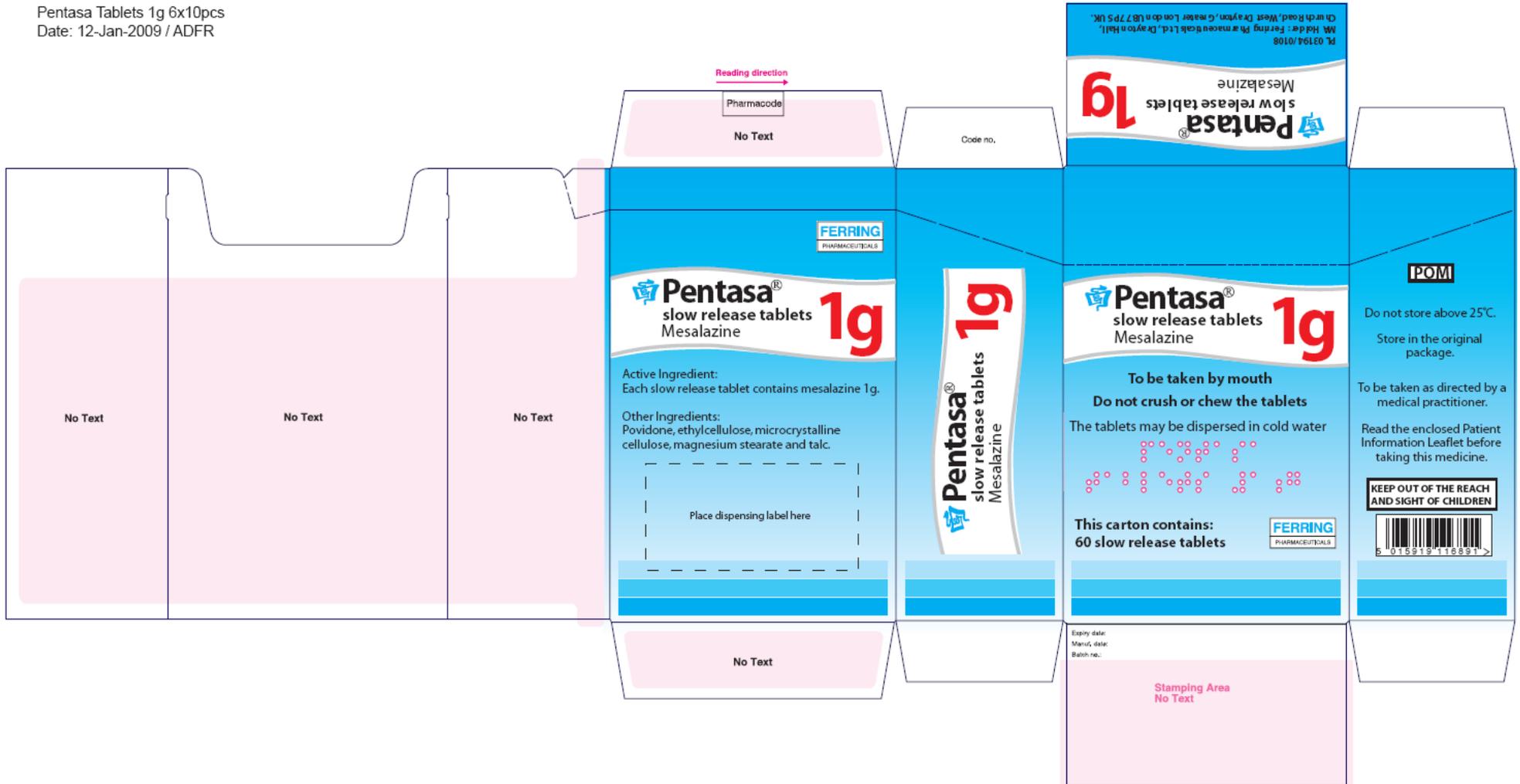
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

**PATIENT INFORMATION LEAFLET**

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

**LABELLING**

Pentasa Tablets 1g 6x10pcs  
Date: 12-Jan-2009 / ADFR



									IVIDX. ZDIIIII	
									CSAT XXXX.XX	
Pentasa® slow release tablets Mesalazine 1g Ferring										
Exp.: Lot.: Mfg.:										
Pentasa® slow release tablets Mesalazine 1g Ferring										
Exp.: Lot.: Mfg.:										

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**Annex 1**

**Our Reference:** PL 03194/0108, Application 10  
**Product:** PENTASA Slow Release Tablets 1g  
**Marketing Authorisation Holder:** Ferring Pharmaceuticals Limited  
**Active Ingredient(s):** Mesalazine

**Type of Procedure:** National  
**Submission Type:** Variation  
**Submission Category:** Type II  
**Submission Complexity:** Standard  
**EU Procedure Number (if applicable):**

**Reason:**

To update section 4.2 (posology) of the Summary of Product Characteristics (SmPC) to include an alternative dosing of once daily, based on the results of a recent clinical trial. As a consequence, the Patient Information Leaflet (PIL) has been updated.

**Linked / Related Variation(s) or Case(s):**

The Assessment Report refers to the Collection ID 150310 and covers the following submissions PL 03194/0044 - 0091.

**Supporting Evidence**

The applicant has submitted the results from one clinical study, as well as an updated SmPC and PIL.

The clinical study is summarised below:

**Primary Objective**

To demonstrate that an oral dose of mesalazine 4 g per day once daily (QD) was non-inferior to the reference regimen, an oral dose of mesalazine 4 g per day in two divided doses (BID) (2 x 2 g per day), in patients with active ulcerative colitis (UC) treated for 8 weeks, in terms of remission evaluated with the Ulcerative Colitis Disease Activity Index [UC-DAI] score  $\leq 1$ . Both treatment groups received a daily enema containing 1 g of mesalazine at bedtime during the initial 4 weeks.

**Primary Endpoint**

Remission after 8 weeks of treatment, defined as UC-DAI score  $\leq 1$ .

**Secondary Endpoints**

Comparison of the following items between the two groups:

- Compliance at Week 8.
- Clinical remission at Week 4, Week 8 and Week 12.
- Treatment failure rates at Week 4 and Week 8 defined as the need for other treatment (i.e. steroids, immunosuppressive or immunomodulating drugs) than those allowed by the protocol. The need for other treatment was judged by investigators. Treatment failure was counted as non-remission.
- Clinical variables (stool frequency and bloody stools) at Week 4, 8 and 12 separately.
- Time to remission according to patient's diary (normal stool frequency and cessation of bleeding).
- Time to cessation of bleeding.
- Improvement at Week 4 and 8 based on UC-DAI score.
- Endoscopic assessment at Week 0 and Week 8.

- Acceptability of the treatment at Week 4 and 8.
- Safety.

### Main criteria for inclusion/exclusion

The patient population was selected to include patients that were 18 years or over with relapsing mild to moderate UC. Patients with a newly diagnosed or relapsing disease, and with a disease extension beyond the rectum and a UC-DAI score between 3 and 8 in the 15 days before inclusion, were included.

Patients that in the previous year had failed to respond to steroids and were non-responsive to rectal 5-ASA therapy, or to oral 5-ASA therapy (>3 g/day for induction) were not to be included

Patient disposition in the trial is shown below:

	QD (%)	BID (%)	Total (%)
Screened patients			100%
Reason for screening failure			
- Patient is not fulfilling inclusion/exclusion criteria			2.3%
- Patient withdrew consent			0.5%
- Other			1.4%
Randomised patients	49.5%	50.1%	100%
Safety Analysis Set	50.5%	49.5%	98.1%
ITT Analysis Set	50.0%	50.0%	98.1%
mITT Analysis Set	44.1%	44.6%	88.6%
Per Protocol Set	39.1%	38.1%	77.2%
Reason for withdrawal before Visit 3:			
- Insufficient response	2.0%	1%	1.5%
- Worsening of UC	1.0%	1.9%	1.5%
- AE	2.0%	2.9%	2.4%
- SAE	2.0%	1.0%	1.5%
- Patient lost to follow up	1.0%	1.0%	1.0%
- Other reasons	4.0%	4.8%	4.4%

### Statistical Methods

#### The Intention-To-Treat Efficacy Population

The Intention-To-Treat (ITT) efficacy population included all randomised patients who received at least one dose of the test product, evaluated for Last Observation Carried Forward (LOCF) and for Observed Cases (OC).

The modified ITT (mITT) population included all patients in the ITT population having evaluable UC-DAI score at Visit 3 (Week 8).

#### The Per-Protocol Efficacy Population

The Per-Protocol (PP) efficacy population included all patients in the ITT population without any major

protocol deviation, evaluated for LOCF and for OC.

Quantitative variables were summarised in tables displaying sample sizes, means, standard deviations, medians and percentiles when appropriate, and extreme values. Qualitative variables were described in terms of frequencies and percentages of the number of individuals examined.

For the primary efficacy endpoint the non-inferiority of the 4 g/ day QD regimen was assessed by calculating the 95% two-sided Confidence Interval (CI) of the difference in remission rates between the QD and BID regimen for the ITT, mITT and PP; LOCF. CI were adjusted on country and computed using Mantel- Haenszel weights. The 4 g/day QD regimen would be non-inferior to the 4 g/day BID regimen if the lower limit of this CI was greater than -15%.

Secondary efficacy endpoints were summarised for the ITT (OC and LOCF) population using descriptive statistics and compared between treatment groups using Cochran-Mantel-Haenszel chi-square d-tests adjusted on country (categorical variables) or analyses of variance with or without repeated measures with country as cofactor.

Time to remission according to patient's diary and time to cessation of bleeding defined as the time between the first dose of the test product and the first bleeding free day were compared between treatment groups using survival analysis adjusted by country (Cox model).

Clinical remission at Week 4, 8 and 12 (defined as normalization of stool frequency, disappearance of bleeding stools and no active disease at Physicians Global Assessment), endoscopic remission at Week 8, mucosal healing based on UC-DAI index (endoscopic sub-score  $\leq 1$ ) at Week 8 and complete remission (UC-DAI score=0) at Week 8 were submitted to the same analysis as the primary analysis computing a two-sided 95% CI of the difference between treatments after adjustment on country.

Correlation coefficients between compliance and other secondary efficacy variables were computed, both groups combined. To measure the strength of the association between the compliance level and quantitative variables, Spearman's rank correlation coefficient were computed. For qualitative variables, the correlation ratio was used.

### **Efficacy Results**

The primary efficacy endpoint of the trial was the rate of remission (UC-DAI score  $\leq 1$ ) at Week 8 of treatment assessed in ITT, mITT and PP populations. Despite the actual sample size being smaller than that planned, non-inferiority was shown in the three statistical analysis subsets. With remission rates of:

- 52.1% in the QD group and 41.8% in the BID group, 95% CI: [3.4; 24.1] in the ITT population.
- 58.8% in the QD group and 46.8% in the BID group, 95% CI: [-2.6; 26.6] in the mITT population.
- 61.0% in the QD group and 48.3% in the BID group, 95% CI: [-2.7; 28.2] in the PP population.

The analysis supported non-inferiority of the 4 g/day QD regimen, compared to the 4 g/day BID regimen. PENTASA 4 g/day (QD) was non-inferior, as well as consistently numerically superior to PENTASA 4 g/day (BID) in all secondary efficacy analyses. The QD regimen was non-inferior for rates of patients achieving clinical remission at:

- Week 4 (clinical remission rate varied from 39.8% to 43.8% in QD group compared to 27.6% to 30.8% in BID group).
- Week 8 (clinical remission rate varied from 45.1% to 50.3% in QD group compared to 40.8% to 44.3% in BID group).

Furthermore, the QD regimen was non-inferior in:

- Rates of patients staying in clinical remission at Week 12 (92.4% in the QD group *versus* 79.4% in the BID group); Rates of complete remission at Week 8 (varied from 31.1% to 35.5% in QD group *versus* from 26.1% to 29.2% in BID group);
- Rate of endoscopic remission (Rachmilewitz score <4) at Week 8 (varied from 62.2% to 70.2% in QD group *versus* from 54.4% to 61.1% in BID group).

In some secondary efficacy analyses, the QD regimen was superior to the BID regimen:

- Normal stools were more frequent at Week 4 (p=0.0133);
- Improvement at Week 8 (decrease of the UC-DAI score of 2 points or more) was more frequent (p=0.0148);
- Time to remission was shorter (p=0.0416);
- Endoscopic Rachmilewitz score was improved at Week 8 (p=0.0030);
- Mucosal healing rates at Week 8 were higher according to UC-DAI index (p=0.0069).

Treatment compliance was similarly high in both treatment groups.

### Safety Results

Similar proportions of patients in both treatment groups - approximately one-third overall - had adverse events (AEs), and treatment-emergent adverse events (TEAE), during the trial (Safety population). The most frequently observed TEAEs were mild or moderate gastrointestinal disorders, in <10% of the patients. No death occurred in the trial. Ten serious AEs (SAEs) were reported in 8 patients; 4 of these SAEs were considered possibly or probably related to the test product (one patient in each treatment group). Over the course of treatment, there were no meaningful differences between the treatment groups in mean clinical safety laboratory parameters, weight, and vital signs, as well as in the frequency of markedly abnormal changes in these safety variables. In conclusion, PENTASA 4 g/day (once-daily dosing) is considered safe and well tolerated

### Conclusions of the study

In active, *mild to moderate* UC, oral PENTASA 4 g/day (once-daily dosing) was non-inferior to PENTASA 4 g/day (in two divided doses) in induction of remission, after 8 weeks of treatment.

Treatment compliance was similarly high with both the QD and the BID treatment regimen.

Both the QD and BID treatment regimens were safe and well tolerated.

### Evaluation

Adequate clinical information has been provided.

The updated sections of the SmPC and the updated PIL are satisfactory.

### Conclusion

The amendments to the SmPC and PIL are acceptable and there are no objections to approval.

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

**Decision** – Approved 26 May 2014