SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Octasa 800 mg Modified Release Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified release tablet contains: 800 mg mesalazine.
Excipient with known effect: 152.8 mg lactose monohydrate, see section 4.4
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-Release Tablet
Red-brown, oblong, modified-release tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Octasa is indicated in adults, children and adolescents above 6 years for:

Ulcerative Colitis:
For the treatment of mild to moderate acute exacerbations. For the maintenance of remission.

Crohn's ileo-colitis:
For the maintenance of remission.

4.2 Posology and method of administration

Posology

Adults

- *Mild acute disease:* 2.4 g (three tablets) once daily or in divided doses, with concomitant corticosteroid therapy to be taken when clinically indicated.
- *Moderate acute disease:* 2.4 g to 4.8 g (three to six tablets) a day in divided doses,

with concomitant corticosteroid therapy where clinically indicated. 2.4 g may be taken once daily or in divided doses. Above 2.4 g should be taken in divided doses.

- *Maintenance therapy:* 1.6 g to 2.4 g *(*two to three tablets) taken once daily or in divided doses.
- The maximum adult dose should not exceed six tablets a day and not exceed 3 tablets taken together at any one time.

Elderly population

The normal adult dosage may be taken unless liver or renal function is severely impaired (see section 4.3 and 4.4). No studies have been carried out in the elderly population.

Paediatric population

There is only limited documentation for an effect in children (age 6-18 years).

Children 6 years of age and older

- *Active disease:* To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day.

- *Maintenance treatment:* To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day.

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

Method of administration: Oral.

The tablets must be swallowed whole preferably with some liquid before food intake. They must not be chewed, crushed or broken before swallowing. If one or more doses have been missed, the next dose is to be taken as usual.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Known hypersensitivity to salicylates
- Severe liver impairment
- Severe renal impairment (GFR less than 30 mL/min/1.73 m^2).

4.4 Special warnings and precautions for use

Blood tests (differential blood count, liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, follow-up tests are recommended

14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional signs appear, these tests should be performed immediately.

Renal impairment

Caution should be exercised in patients with raised serum creatinine or proteinuria. The possibility of mesalazine-induced nephrotoxicity should be suspected in patients developing impairment of renal function during treatment. Patients need to remain well hydrated whilst taking Octasa to reduce the risk of crystalluria and consequential kidney damage.

Treatment with Octasa should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.

Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Blood dyscrasia

Serious blood dyscrasia have very rarely been reported. Octasa therapy should be stopped immediately if there is suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, bruising, purpura, anemia, persistent fever or sore throat), and patients should seek immediate medical advice.

Hepatic impairment

There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine. Caution is recommended if Octasa is administered to patients with liver impairment. Blood tests (liver function parameters such as ALT or AST) should be performed prior to and during treatment, at the discretion of the treating physician. As a

guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every 3 months. If additional symptoms occur, these tests should be performed immediately.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have rarely been reported with Octasa. In case of previous mesalazine-induced cardiac hypersensitivity Octasa must not be reintroduced. Caution should be taken in patients with previous myo- or pericarditis of allergic background regardless of its origin.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Pulmonary disease

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during treatment with Octasa.

Adverse drug reactions to Sulphasalazine

Patients with a history of adverse drug reactions to sulphasalazine therapy should be kept under close medical supervision. Treatment must be stopped immediately if acute symptoms of intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache and rash.

Gastric and duodenal ulcers

In case of existing gastric or duodenal ulcers treatment should begin with caution based on theoretical grounds.

Tablets in stool

A limited number of reports of intact tablets in the stool have been received. What appear to be intact tablets may in some cases represent largely empty shells of the coated tablets. If intact tablets are observed in the stool repeatedly, the patient should consult his/her physician.

Elderly population

Use in the elderly should be handled with caution and the product should only be prescribed to patients having a normal or non-severely impaired liver and renal function, see section 4.3.

Paediatric population

There is only limited documentation for an effect in children (age 6-18 years), see section 4.2.

Pharmaceutical excipients of special interest

Intolerance to carbohydrates

With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, i.e. is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine or thioguanine should be taken into account. As a result, life-threatening infection can occur. Patients should be closely observed for signs of infection and myelosuppression. Haematological parameters, especially the leucocyte, thrombocyte, and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy, see section 4.4. If white blood cells are stable after 1 month, testing every 4 weeks for the following 12 weeks followed by 3 monthly monitoring intervals appears to be justified.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of Octasa in pregnant women. However, data on a limited number (627) of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiologic data are available.

In one single case, after long-term use of a high dose of mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects, with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Octasa should only be used during pregnancy if the potential benefit outweighs the

possible risk.

Breast-feeding
N-acetyl-mesalazine and, to a lesser degree, mesalazine are excreted in breast milk. The clinical significance of this has not been determined. Only limited experience in women during lactation is available to date. Hypersensitivity reactions like diarrhoea in the infant cannot be excluded. Therefore, Octasa should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, the breast-feeding should be discontinued.

Fertility
No effects on fertility have been observed.

4.7 Effects on ability to drive and use machines

Octasa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Octasa 800 mg Modified Release Tablets have been evaluated in 140 patients with mild to moderate active ulcerative colitis in one controlled study lasting for 10 weeks comparing safety and efficacy versus another 141 patients receiving placebo. Treatment related undesirable effects in the Octasa group with the highest reporting rate were worsening of ulcerative colitis (3.6%), haematuria (2.9%), and ketonuria (2.1%). All undesirable effects with Octasa 800 mg Modified Release Tablets were of mild to moderate severity. Discontinuations due to adverse reactions occurred in 8.6% of patients in the Octasa group and in 21.3% of patients in the placebo group. Most of the drug related reactions that led to study drug discontinuation were related to worsening of ulcerative colitis.

Organ specific adverse drug reactions affecting the heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue have been reported.

Treatment must be stopped immediately if acute symptoms of intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache and rash.

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

b) Tabulated summary of adverse reactions

In addition to the undesirable effects reported above in a clinical trial with Octasa 800 mg Modified Release Tablets, undesirable effects relevant for the labeling reported from eight (8)

double-blind and five (5) open clinical studies with 739 patients treated with Octasa 400 mg MR Tablets are listed below.

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known**
Blood and lymphatic system disorders		eosinophilia (as part of an allergic reaction)		altered blood counts (aplastic anemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia)	
Immune system disorders				hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Nervous system disorders		paresthesia	headache, dizziness	peripheral neuropathy	Idiopathic intracranial hypertension (see section 4.4)
Cardiac disorders			myocarditis, pericarditis		
Respiratory, thoracic and mediastinal disorders				allergic and fibrotic lung reactions (including dyspnoea, cough bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), interstitial pneumonia, eosinophilic pneumonia, lung disorder	pleurisy

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Frequency not known
Gastrointestinal disorders	dyspepsia		abdominal pain, diarrhoea, flatulence, nausea, vomiting	acute pancreatitis	
Hepato-biliary disorders				changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis	
Skin and subcutaneous tissue disorders	rash	urticaria, pruritus	Photosensitivity*	alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders				myalgia, arthralgia	lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Frequency not known
Renal and urinary disorders				Impairment of renal function including acute and chronic interstitial nephritis, renal insufficiency, nephrotic syndrome and renal failure which may be reversible on early withdrawal	Nephrolithiasis**
Reproductive system and breast disorders				oligospermia (reversible)	
General disorders and administration site conditions		pyrexia, chest pain,			intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms of underlying disease
Investigations					blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased

* see section c)

** see section 4.4 for further information

c) Description of selected adverse reactions

An unknown number of the above mentioned undesirable effects are probably associated to the underlying IBD rather than Octasa/mesalazine medication. This holds true especially for gastrointestinal undesirable effects, arthralgia, and alopecia.

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care, see section 4.4.

Under co-administration of mesalazine with myelosuppressive drugs, such as azathioprine, or 6-MP, or thioguanine, life-threatening infection can occur, see section 4.5.

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

d) Paediatric population

There is only limited safety experience with the use of Octasa in the paediatric population. It is expected that the target organs of possible adverse reactions in the paediatric population are the same as for adults (heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are rare data on overdose (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive.

In principle, the signs and symptoms would be expected to be similar to those observed in cases of salicylate intoxication: mixed acidosis-alkalosis, hyperventilation, pulmonary oedema, dehydration as a result of sweating and vomiting, and hypoglycaemia.

Treatment

For mixed acidosis-alkalosis: restoration of the acid-base balance in line with the specific situation and replacement of electrolytes.

For dehydration due to sweating and vomiting: administration of fluids.

For hypoglycemia: glucose administration.

In addition gastric lavage and intravenous infusion of electrolytes to promote diuresis.

There is no known antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents; ATC code: A07E C02.

Mechanism of action

Octasa contains mesalazine, also known as 5-aminosalicylic acid, which has an anti-inflammatory effect through a mechanism that has not yet been fully clarified. Mesalazine has been shown to inhibit LTB4-stimulated migration of intestinal macrophages and thus may reduce intestinal inflammation by restricting migration of macrophages to inflamed areas. The production of pro-inflammatory leukotrienes (LTB4 and 5-HETE) in macrophages of the intestinal wall is inhibited. Mesalazine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

Pharmacodynamic effects

Under trial conditions mesalazine inhibited the cyclooxygenase and thus, the release of thromboxane B_2 and prostaglandin E_2, but the clinical meaning of this effect is still unclear. Mesalazine inhibits the formation of platelet activating factor (PAF). Mesalazine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals.

Clinical efficacy and safety

Octasa 800 mg Modified Release Tablets have been evaluated in 140 patients with mild to moderate active ulcerative colitis in one controlled study lasting for 10 weeks comparing safety and efficacy versus placebo. This indication was also investigated in seven controlled and three open clinical trials including 787 patients, of whom 559 received Octasa 400 mg Modified Release Tablets. Three studies were placebo-controlled, one of which also compared the efficacy of Octasa to another proprietary oral mesalazine product. Five studies were performed without comparator. The studies included dose ranging of Octasa. One study compared the efficacy of mesalazine versus sulfasalazine. The studies included dose ranging of Octasa from 1.2 g/day to 4.8 g/day. One study used computerised morphometry to assess the efficacy of Octasa compared with a prednisolone enema. These studies established the safety and efficacy of Octasa for the treatment of mild to moderate acute UC at daily doses of 2.4 – 4.8 g mesalazine.

Maintenance of remission of ulcerative colitis

This indication was studied in five controlled and two open clinical trials involving 677 patients, of whom 406 received Octasa 400 mg Modified Release Tablets. Octasa treatment was compared to sulfasalazine in three studies, to another proprietary oral mesalazine product in one study, and to placebo in one study. The dosage varied from 0.8 - 4.4 g mesalazine per day. These studies established the safety and efficacy of Octasa for the maintenance of remission of UC at daily doses of 1.6 – 2.4 g mesalazine.

Maintenance of remission of Crohn's ileo-colitis

This indication was studied in one double blind, one retrospective and two open clinical studies involving 336 patients, of whom 159 received Octasa 400 mg Modified Release Tablets. Octasa treatment was compared to sulfasalazine in one study and to placebo or no specific treatment in three studies. Two studies confirmed efficacy in preventing post-operative recurrence of Crohn's disease.

These studies support the safety and efficacy of Octasa in the treatment of quiescent Crohn's disease of the terminal ileum and colon including post-operative patients at a daily dose of 2.4 g mesalazine.

5.2 Pharmacokinetic properties

Absorption

Octasa tablets are coated with a pH-responsive polymer which enables the release of mesalazine only at a pH above 7, i.e. within the terminal ileum and colon, which are the main sites of inflammation in IBD. After any initial disruption of the coating mesalazine will continue to be released irrespective of the pH. Octasa tablets have been designed to be minimize the absorption of of mesalazine from the digestive tract.

After a single dose of 2.4 g of mesalazine (3 Octasa 800 mg GR Tablets) in healthy volunteers under fasting conditions quantifiable amounts (> 2.00 ng/mL) of mesalazine were observed in plasma after 4.5 h (median t_{lag}). The geometric mean C_{max}-value of mesalazine was 387.86 ng/mL with a median t_{max} of 14.0 h, whereas that of N-acetyl mesalazine was 971.09 ng/mL with an identical median t_{max}, i.e. 14.0 h.

Based on the recovery of unchanged mesalazine and the main metabolite N-acetyl mesalazine in collected urine after oral fasted administration approximately 23% of the dose (more than 95% as metabolite) was excreted renally within 60 h.

Following concomitant food intake in the same study, a single dose of 2.4 g of mesalazine resulted in quantifiable amounts of mesalazine after 14.5 h (median t_{lag}). The geometric mean C_{max}-value of mesalazine was 653.56 ng/mL with a median t_{max} of about 30.0 h, whereas that of N-acetyl mesalazine was 1245.46 ng/mL with a median t_{max} of 30.0 h.

Based on the recovery of unchanged mesalazine and the main metabolite N-acetyl mesalazine in collected urine after oral fed administration, approximately 23% of the dose (more than 95 % as metabolite) was excreted renally within 60 h.

Following concomitant food intake the C_{max}-values of mesalazine increased 1.69-fold, and the extent of exposure ($AUC_{0\text{-}tlast}$) increased 1.23-fold. Concerning N-acetyl mesalazine after concomitant food intake the C_{max}-values increased 1.28-fold, whereas its extent of exposure remained practically unchanged.

Distribution

About 43% mesalazine and about 78% N-acetyl mesalazine are bound to plasma proteins. Approximately 77 % of the administered dose remains in the gut lumen and the mucosal tissue. The mean apparent volume of distribution per kg of body weight (Vd_w) was 147.73 L/kg (geometric mean: 76.06 L/kg) after a single dose of 2.40 g of mesalazine (3 GR tablets of Octasa 800 mg) in healthy volunteers under fasting conditions. Based upon the absorption of 23.2% of the administered dose, this parameter is equal to 34.27 L/kg (geometric mean: 17.65 L/kg).

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Low concentrations of mesalazine and N-acetyl mesalazine have been detected in human breast milk. The clinical significance of this has not been determined.

Biotransformation

Mesalazine is metabolised both by the intestinal mucosa and the liver to the inactive metabolite N-acetyl mesalazine. About 96% of the drug recovered in the urine after oral administration is found as the main metabolite N-acetyl-mesalazine.

Elimination
The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its N-acetyl metabolite. The geometric mean of total apparent clearance of mesalazine after administration of 2.40 g of mesalazine (3 GR tablets of Octasa 800 mg) in healthy volunteers under fasting conditions was about 318 L/h (geometric mean, CV% = 137.67%, intersubject). The median elimination half-life was 17 h ranging from 10 to 50 h.
About 23% of the total dose administered was recovered in the urine within 60 h after fasted administration mainlyas N-acetyl mesalazine and as the parent compound (about 1%).

Linearity/non-linearity
In a cross-over design with 3 test periods and 3 ascending oral doses of Octasa 400 mg GR Tablets administered 6 hourly over 4 consecutive doses (total daily dose of mesalazine: 3200, 4800, 6400 mg) it was shown that the absorption and elimination kinetics for mesalazine are dose independent for the 3 doses evaluated. For each dose, about ¾ of the dose was available for the therapeutic activity for the colon. Only about ¼ of each dose was absorbed and excreted in the urine, primarily as the metabolite. Based on urine drug excretion, plasma drug Cmax's and the combined plasma AUC's, there was a linear dose response for the 3 Octasa tablet doses. The clinical performance of Octasa should be similar for the range of doses evaluated in this study.

Pharmacokinetic/pharmacodynamic relationship(s)
No specific studies have been performed.

5.3 Preclinical safety data

Preclinical data with mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity or toxicity to reproduction.

Renal toxicity (renal capillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Sodium starch glycolate (Type A)

Magnesium stearate (vegetable origin)

Talc E553b

Povidone E1201

Methacrylic acid – methyl methacrylate copolymer (1:2)

Triethyl citrate
Iron oxides E172
Macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25 °C. Store in the original package to protect from moisture.

6.5. Nature and contents of container

Octasa 800 mg Modified Release Tablets are available in PVC/aluminium blisters, each containing ten tablets.
The blisters are packed in cartons containing either 60, 90 or 180 tablets.

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Wellingore Hall
Wellingore
Lincolnshire, LN5 0HX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36633/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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