PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrOCTASA™

Mesalamine *

Tablet (Delayed-Release), 800 mg, Oral

Lower Gastrointestinal Anti-Inflammatory

Tillotts Pharma AG

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Switzerland

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* also known as 5-aminosalicylic acid (5-ASA)

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Octasa (800 mg; mesalamine [also known as 5-aminosalicylic acid] delayed-release tablets) is indicated for:

- the treatment of moderately active ulcerative colitis

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of Octasa has not been established in children. Octasa (800 mg tablet) is contraindicated in patients unable to swallow an intact tablet.

1.2 Geriatrics

No data are available to Health Canada, therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Octasa (800 mg tablet) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with a history of sensitivity to salicylates
- Severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS)
- Severe renal impairment (GFR < 30 mL/min/1.73 m2); (see 7 WARNINGS AND PRECAUTIONS)
- Patients with existing gastric or duodenal ulcer
- Patients with urinary tract obstruction
- Patients unable to swallow the intact tablet

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **History of adverse drug reactions to sulfasalazine**: Patients with a history of adverse drug reactions to sulfasalazine 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.
- **Blood system:** Serious blood dyscrasia has very rarely been reported. Octasa therapy should be stopped immediately if there is a 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. It is recommended that hematological investigations (differential blood count) are performed prior to initiation of Octasa and whilst on therapy, at the discretion of the treating physician (see 7 WARNINGS AND PRECAUTIONS).
- **Renal:** Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure has been reported in patients taking mesalamine products. Octasa (800 mg tablet) is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS). It is recommended that all patients have an evaluation of their renal function prior to initiation of Octasa therapy and repeatedly whilst on therapy (see 7 WARNINGS AND PRECAUTIONS).
- **Pulmonary:** Patients with pulmonary disease, in particular asthma, should be very carefully monitored during treatment with Octasa.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely. Abrupt discontinuation of Octasa (800 mg tablet) is not recommended, and may result in relapse. It is important for patients to comply with the dosage prescribed by their doctors; by doing so, the risk of relapse can be substantially reduced.

4.2 Recommended Dose and Dosage Adjustment

For the treatment of moderately active ulcerative colitis:

Adults

Usual daily adult dose is 6 Octasa (800 mg tablet) tablets (4.8 g), taken orally once daily or in divided doses with or without food.

Geriatrics (≥65 years)
The normal adult dose can be taken unless hepatic or renal function is severely impaired (see 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS). No clinical studies have been carried out in geriatric population.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

- Swallow tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact, to protect the active ingredient until it reaches the terminal ileum, where the tablet coating dissolves and the contents of the tablet are released into the terminal

ileum and colon.

- Take Octasa (800 mg tablet) tablets only as prescribed. Do not change the number or frequency of tablets ingested without first consulting your physician.
- What appears to be intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, consult your physician.

4.5 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double the dose.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Delayed-Release tablets, 800 mg	acetone, ferric oxide yellow, ferric oxide red, isopropyl alcohol, lactose monohydrate, macrogol 6000, magnesium stearate, methacrylic acid-methylmethacrylate copolymer (1:2), povidone, sodium starch glycolate (type A), talc and triethylcitrate.

Octasa 800 mg delayed-release tablets are available for oral administration as coated red/brown oblong tablets.

Each delayed-release tablet contains 800 mg mesalamine. Octasa consist of a conventional disintegrating tablet core formulation with a film coat containing a copolymer with a pH dependant dissolution behaviour as follows: the delayed-release tablets are designed to resist to drug substance release in acid media of the stomach and small intestine (tested at pH 1.0 and pH 6.4), whereas disintegration and drug substance release needs to occur at pH 7 (tested at pH 7.2) to ensure delivery of mesalamine at the target site, i.e. the terminal ileum and beyond.

Octasa 800 mg delayed-release tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing either 20 or 180 tablets.

7 WARNINGS AND PRECAUTIONS

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

Octasa (800 mg tablet) and other mesalamine-containing products have differences in formulation and release characteristics that may lead to differences in concentrations of mesalamine delivered to the colon. If it is deemed necessary to switch from one mesalamine containing product to another mesalamine-containing product, the prescriber should carefully assess the overall benefit-risk analysis based on the patient's clinical conditions and on all available information for the various mesalamine-containing products.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Mesalamine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have rarely been reported with Octasa. In case of a suspected mesalamine-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.

Gastrointestinal

Acute exacerbation of the symptoms of colitis, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by nausea has been reported in patients in controlled clinical trials of Octaca (800 mg).

Octasa (800 mg) is contraindicated in patients with existing gastric or duodenal ulcers (see 2 CONTRAINDICATIONS).

Hematologic

Serious blood dyscrasia has very rarely been reported. Octasa therapy should be stopped immediately if there is a 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. It is recommended that hematological investigations (differential blood count) are performed prior to initiation of Octasa and whilst on therapy, 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.

Hepatic/Biliary/Pancreatic

Caution should be exercised when using Octasa (800 mg tablet) (or other compounds that contain or are converted to mesalamine or its metabolites) in patients with hepatic dysfunction.

In assessing liver complications, it should be kept in mind that these are frequently associated with ulcerative colitis.

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with mesalamine (also known as 5-ASA) products. Therefore, Octasa

(800 mg tablet) is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and Octasa (800 mg tablet) should only be used if the expected benefit clearly outweighs the risks to the patients. 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.

Immune

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Octasa (800 mg tablet) or to other compounds that contain, or are converted to, mesalamine.

Monitoring and Laboratory Tests

It is recommended that all patients have an evaluation of their renal function (urinary status via dip sticks); hepatic function (blood tests such as ALT or AST) as well as hematological investigations (differential blood count) prior to initiation of Octasa therapy and repeatedly whilst on therapy.

Renal

Reports of renal impairment, including minimal change nephropathy, acute or chronic interstitial nephritis have been associated with mesalamine products and pro-drugs of mesalamine. Octasa (800 mg tablet) is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, caution should be exercised and Octasa (800 mg tablet) should be used only if the benefits outweigh the risks.

Urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. Caution should be exercised in patients with raised serum creatinine or proteinuria. The possibility of mesalamine-induced nephrotoxicity should be suspected in patients developing impairment of renal function during treatment.

It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment.

As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. Short monitoring intervals early after the start of Octasa therapy will discover rare acute renal reactions. In the absence of an acute renal reaction monitoring intervals can be extended to every 3 months and then annually after 5 years. If additional laboratory or clinical signs of renal impairment appear, these tests should be performed immediately. Treatment with Octasa should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Reproductive Health: Female and Male Potential

- **Fertility**

  No effects on fertility have been observed.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies of Octasa (800 mg tablet) use in pregnant women. Limited published data on the class of mesalamine products show an increased rate of preterm birth, stillbirth and low birth weight. These adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Mesalamine crosses the placenta. Animal reproduction studies of mesalamine found no evidence of fetal harm.

Octasa (800 mg tablet) should only be used during pregnancy if the potential benefit outweighs the possible risk.

7.1.2 Breast-feeding

Literature reports indicate that, following oral or rectal administration of mesalamine-containing products to lactating women, small amounts of mesalamine (also known as 5-ASA) and higher concentrations of the metabolite N-acetyl-5-ASA are found in breast milk. The clinical significance of this has not been determined. Only limited experience during lactation in women is available to date.

When Octasa is used in nursing women, infants should be monitored for changes in stool consistency. If the infant develops diarrhea, breastfeeding should be discontinued. Cases of diarrhea in breastfed infants exposed to mesalazine have been reported.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Use in elderly people should be handled with caution and Octasa (800 mg tablet) should only be prescribed to elderly people having a normal or non-severely impaired hepatic or renal function, see 2 CONTRAINDICATIONS.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Octasa (800 mg tablet) is generally well tolerated. 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. The most commonly reported adverse reactions were ulcerative colitis followed by haematuria and ketonuria.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Octasa 800 mg delayed-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. 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%).

Table 1 enumerates treatment related adverse reactions that occurred at a frequency of ≥1% in the Octasa and placebo treated groups. All adverse reactions associated with the use of Octasa 800 mg delayed-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 adverse reactions that led to study drug discontinuation were related to worsening of ulcerative colitis.

Table 1 – Adverse drug reactions related to Octasa 800 mg delayed-release tablets in mild to moderately active UC at a frequency of ≥1% versus placebo

	Octasa 800 mg n = 140 (%)	**placebo n = 141 (%)**
Blood and lymphatic system disorders		
Anaemia	1.4	0.7
Eosinophilia	1.4	0.0
Leukocytosis	1.4	0.0
Macrocytosis	1.4	0.0
Monocytopenia	1.4	2.8
Gastrointestinal disorders		
Worsening of ulcerative colitis	3.6	8.5
Haemorrhoids	1.4	0.0
Hepatobiliary disorders		
Hyperbilirubinaemia	1.4	1.4
Nervous system disorders		
Headache	1.4	1.4
Renal and urinary disorders		
Haematuria	2.9	2.1
Ketonuria	2.1	0.7

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment-related adverse drug reactions were reported infrequently (less than 1%) by patients with mild to moderate active ulcerative colitis treated with Octasa 800 mg delayed-release tablets:

Blood and lymphatic disorders: hypochromasia, leukopenia, thrombocytopenia

Cardiac disorders: bradycardia, tachycardia

Gastrointestinal disorders: dyspepsia, gastrointestinal pain, upper abdominal pain

General disorders and administration site conditions: pyrexia

Hepato-biliary disorders: hypertransaminasaemia

Metabolism and nutrition disorders: hyperuricaemia

Musculoskeletal and connective tissue disorders: athralgia, myalgia

Renal and urinary disorders: azotaemia

Reproductive system and breast disorders: menstrual disorder

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: rash, rosacea

Vascular disorders: hypertension

8.5 Post-Market Adverse Reactions

In addition to the adverse events reported above in the clinical trial involving Octasa (800 mg tablet), the following adverse events have been reported in literature reports, or foreign and domestic marketing experience with Octasa (800 mg tablet) or other products that contain or are metabolized to mesalamine. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The relationship of the reported events to Octasa (800 mg tablet) is unclear in many cases, and some may be part of the clinical presentation of ulcerative colitis.

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

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, pleurisy, lung disorder

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, alopecia

Musculoskeletal, connective tissue and bone disorders: Myalgia, arthralgia, lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia

Renal and urinary disorders: Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, nephrotic syndrome, renal failure which may be reversible on early withdrawal

Reproductive system and breast disorders: Oligospermia (reversible)

General disorders and administration site conditions: Intolerance to mesalamine with C-reactive protein increased and/or exacerbation of symptoms of underlying disease, pyrexia, chest pain

Investigations: Blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- In patients who are concomitantly treated with azathioprine, or 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine or thioguanine should be taken into account (see 9.4 Drug-Drug Interactions). 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 7 WARNINGS AND PRECAUTIONS. 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.

9.2 Drug Interactions Overview

No drug interaction studies have been performed with Octasa (800 mg tablet). There is weak evidence that mesalamine might decrease the anticoagulant effect of warfarin.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

In patients who are concomitantly treated with azathioprine or 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine or 6-mercaptopurine or thioguanine should be taken into account (**Table 2**).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Azathioprine 6-Mercaptopurine	CT	Significant increases in mean whole blood 6-thioguanine nucleotide concentrations from baseline at most time points	Caution is warranted and therapeutic concentration monitoring is recommended

CT = Clinical Trial

9.5 Drug-Food Interactions

Following concomitant food intake, a single dose of 2.4 g of mesalamine (3 Octasa delayed-release tablets) resulted in quantifiable amounts of mesalamine after 14.5 h (median t_{lag}) compared to 4.5 h (median t_{lag}) under fasting conditions. Thus, concomitant food intake leads to a prolongation of the median lag time of around 10 hours.

The C_{max}-values of mesalamine increased 1.69-fold, and the extent of exposure ($AUC_{0\text{-}tlast}$) increased 1.23-fold following concomitant food intake.

Similarly, the C_{max}-values of N-acetyl mesalamine increased 1.28-fold after concomitant food intake, whereas its extent of exposure remained practically unchanged.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Octasa contains mesalamine (also known as 5-aminosalicylic acid) which has an anti-inflammatory effect through a mechanism that has not yet been fully clarified. Mesalamine 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. Recently mesalamine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

10.2 Pharmacodynamics

Under trial conditions mesalamine 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. Mesalamine inhibits the formation of platelet activating factor. Mesalamine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals.

10.3 Pharmacokinetics

Table 3 - Summary of Octasa 800 mg Pharmacokinetic Parameters in healthy volunteers under fasting condition

	C_{max} (geometric mean)	T_{max} (median)	$t_{½}$ (h) (median)	$AUC_{0-\infty}$	CL (geometric mean)	Vd (geometric mean)
Single dose	387.86 ng/mL	14.0 h	17 h	7553.00	318 L/h	76.06 L/kg

Absorption

Octasa tablets are coated with a pH-responsive polymer which enables the release of mesalamine only at a pH above 7, i.e. within the terminal ileum and colon. Thus mesalamine can be available to the whole colon. After any initial disruption of the coating mesalamine will continue to be released irrespective of the pH. Octasa tablets have been designed to minimize the systemic absorption of mesalamine from the digestive tract.

After a single dose of 2.4 g of mesalamine (3 Octasa 800 mg delayed-release tablets) in healthy volunteers under fasting conditions quantifiable amounts (> 2.00 ng/mL) of mesalamine were observed in plasma after 4.5 h (median t_{lag}). The geometric mean C_{max}-value of mesalamine was 387.86 ng/mL with a median t_{max} of 14.0 h, whereas that of N-acetyl-5-aminosalicylic acid was 971.09 ng/mL with an identical median t_{max}, i.e. 14.0 h.

Based on the recovery of unchanged mesalamine and the main metabolite N-acetyl-5-aminosalicylic acid 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 mesalamine resulted in quantifiable amounts of mesalamine after 14.5 h (median t_{lag}). The geometric mean C_{max}-value of mesalamine was 653.56 ng/mL with a median t_{max} of about 30.0 h, whereas that of N-acetyl-5-aminosalicylic acid was 1245.46 ng/mL with a median t_{max} of 30.0 h.

Based on the recovery of unchanged mesalamine and the main metabolite N-acetyl-5-aminosalicylic acid 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 mesalamine increased 1.69-fold, and the extent of exposure ($AUC_{0\text{-}tlast}$) increased 1.23-fold. Concerning N-acetyl-5-aminosalicylic acid after concomitant food intake the C_{max}-values increased 1.28-fold, whereas its extent of exposure remained practically unchanged.

Distribution:

About 43% mesalamine and about 78% N-acetyl-5-aminosalicylic acid 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 mesalamine (3 delayed-release 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).

Low concentrations of mesalamine and N-acetyl-5-aminosalicylic acid have been detected in human breast milk. The clinical significance of this has not been determined.

Metabolism:

Mesalamine is metabolised both by the intestinal mucosa and the liver to the inactive metabolite N-acetyl-5-aminosalicylic acid. About 96% of the drug recovered in the urine after oral administration is found as the main metabolite N-acetyl-5-aminosalicylic acid.

Elimination

The elimination of mesalamine is essentially urinary and faecal in the form of mesalamine and its N-acetyl metabolite. The geometric mean of total apparent clearance of mesalamine after

administration of 2.40 g of mesalamine (3 delayed-release 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 mainly as N-acetyl-5-aminosalicylic acid and as the parent compound (about 1%).

11 STORAGE, STABILITY AND DISPOSAL

Do not store above 25°C. Store in the original package.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

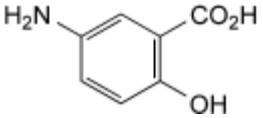
Drug Substance

Proper name: Mesalamine (USAN)
[also known as 5- aminosalicylic acid (5-ASA)]
Mesalazine (INN, Ph. Eur., BP)

Chemical name: 5-amino-2-hydroxybenzoic acid

Molecular formula and molecular mass: $C_7H_7NO_3$ 153.1

Structural formula:



Physicochemical properties: Mesalamine is an almost white to light pink/grey/brown powder or crystals that decomposes at 280°C and is very slightly soluble in water. The pH of 2.5% aqueous suspension is 3.5-4.5. pKa value: 5.8.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

TP0203 was a double blind, randomized, placebo controlled trial. Two hundred eighty one (281) male and female patients were randomly assigned to two treatment groups in a 1:1 ratio.

Adult patients (≥18 years) with a documented diagnosis of Ulcerative Colitis (UC) were eligible to participate if they met the following criteria: (1) disease extending at least 15 cm from the anal verge and (2) mildly to moderately active UC defined by a modified Ulcerative Colitis Disease Activity Index (UCDAI) score of 4 to 10 with a sigmoidoscopy component score ≥2 and a rectal bleeding component score ≥1.

One hundred forty (140) subjects received Octasa 4.8 g/day (3 x 800 mg tablets) b.i.d., and one hundred forty one (141) subjects received placebo. The study treatment was 10 weeks. All treatment regimens were orally administered, with or without food. Subjects randomized to the Octasa 4.8 g/day treatment group received three Octasa 800 mg delayed-release tablets in the morning and three Octasa 800 mg delayed-release tablets in the evening. Subjects randomized to the placebo treatment group received three placebo tablets in the morning and three placebo tablets in the evening.

Treatment and control groups were similar with respect to demographic characteristics such as age (mean 42.35 ± 14.25 years and 40.41 ± 13.80 years, respectively, range 18.5 to 79.4 years). The subjects were either Caucasian (about 80%) or Asian (about 20%) in ethnic origin. Approximately 60% of the subjects were male (**Table 4**).

Table 4 - Summary of patient demographics for clinical trials in mild to moderately active ulcerative colitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TP0203 (ITT)	Double blind, randomised, placebo controlled	Octasa 800 mg delayed-release tablets (4.8 g/day) orally for 10 wks or placebo for 10 wks	Octasa 800 mg delayed-release tablets n=140 placebo n=141	Octasa 800 mg delayed-release tablets: 42.35 ± 14.25 years Placebo: 40.41 ± 13.80 years, (18.5 -79.4 years)	M/F (1:1 ratio)

Efficacy evaluations included clinical symptoms, flexible sigmoidoscopy, determination of UC disease activity assessment index measured by the modified UC-DAI and Ulcerative Colitis Clinical Score (UCCS). Efficacy analyses were performed on the intent-to-treat (ITT) analysis set which included all randomised subjects.

14.2 Study Results

The percentage of patients with mild to moderately active ulcerative colitis who were classified as a treatment success after 10 weeks of Octasa therapy based on the intent-to-treat (ITT) study population are presented in **Table 5**.

Table 5 - Summary of primary endpoints at week 10 (Intent-to-treat population; ITT)

Primary Endpoints	Octasa 800 mg (N=140)	Placebo (N=141)	p-value
Clinical remission at week 10	57 (40.7%)	30 (21.3%)	<0.001
Endoscopic remission at week 10	73 (52.1%)	52 (36.9%)	0.010

Clinical remission and endoscopic remission at week 10 were considered as primary measures of efficacy. For the ITT population, clinical remission at week 10 was achieved in 57 (40.7%) of the subjects who received Octasa 800 mg delayed-release tablets and 30 (21.3%) of the subjects who received placebo (p<0.001; 95% CI 8.6%, 29.6%). For endoscopic remission at week 10, this was achieved in 73 (52.1%) of the subjects who received Octasa 800 mg delayed-release tablets and 52 (36.9%) of the subjects who received placebo (p=0.010; 95% CI 3.6%, 26.3%).

A similar trend was observed at week 6. For the ITT population, clinical remission at week 6 was observed in 42 (30.0%) of the subjects who received Octasa 800 mg delayed-release tablets and 29 (20.68%) of the subjects who received placebo. However, statistical significance was not achieved at

week 6 (p=0.069; 95% CI of the between group difference = [-0.7%, 19.43%]). Endoscopic remission at week 6 was achieved in 64 (45.7%) of the subjects who received Octasa 800 mg delayed-release tablets and 35 (24.8%) of the subjects who received placebo (p<0.001; 95% CI 9.7%, 31.3%).

Results of key secondary endpoints at week 10 (ITT) are presented in **Table 6**.

Table 6 - Summary of secondary endpoints at week 10 (Intent-to-treat population; ITT)

Secondary Endpoints	Octasa 800 mg (N=140)	Placebo (N=141)	p-value
Improvement at week 10	62.9%	40.4%	<0.001
Change in modified UC-DAI[a]	-3.8±2.3	-2.1±2.7	<0.001
Change in flexible proctosigmoidoscopic score[a]	-0.8±0.8	-0.5±0.7	0.002
Change in stool frequency score[a]	-0.9±0.9	-0.3±1.1	<0.001
Change in rectal bleeding score[a]	-1.0±0.8	-0.5±0.9	<0.001
Change in PGA[a]	-0.8±0.9	-0.4±0.8	<0.001
Change in UCCS[a]	-3.2±2.5	-1.5±3.0	<0.001

[a]Mean±SD of change from baseline to the last post-randomization score obtained up to and including End of Treatment assessment.

Results of this clinical study (TP0203) support the efficacy of Octasa 800 mg delayed-release tablets in the treatment of patients with moderate UC for both clinical and endoscopic remission at week 10.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity:
Mesalamine has low acute oral toxicity, as tested in rats and dogs. The oral median lethal dose (LD_{50}) of mesalamine in rats was determined to be 4594 mg/kg. In dogs, the minimum dose causing emesis was 577 mg/kg. No dogs died or were sacrificed moribund up to the maximum dose tested (6000 mg/dog, equivalent to 750 mg/kg), and thus, the oral LD_{50} in dogs was considered to be >750 mg/kg.

Repeat-Dose Toxicity:
The principle target organs of mesalamine toxicity are the kidneys and gastrointestinal (GI) tract as determined in studies conducted in rats. In a 2-week oral toxicity study in rats, necrosis, ulceration, and inflammation in the glandular stomach were observed at doses of 360 and 1080 mg/kg/day. Renal papillary necrosis accompanied by pyelonephritis of the adjacent parenchyma was also observed at a dose of 1080 mg/kg/day. At this dose, one female animal died as a result of renal failure complicated by gastric mucosal injury. Renal papillary necrosis and gastric ulceration and inflammation have also been observed at oral doses of 360 and 480 mg/kg/day in other studies in rats, including a 4-week toxicity study, a two-year carcinogenicity study, and two reproductive toxicity studies. The no-observed-adverse-effect level (NOAEL) for the oral toxicity of mesalamine in rats was considered to be 120 mg/kg/day.

In rabbits, oral administration of mesalamine for 2 weeks at a dose of 1080 mg/kg/day resulted in reduced food consumption (females), diarrhoea (males), and slight increases in urinary measurements of protein, bilirubin, acetone, and urobilinogen. No histological changes were observed in any organs at any dose level. The NOAEL for the oral toxicity of mesalamine in rabbits was determined to be 360 mg/kg/day.

In dogs, no compound-related adverse effects were observed at doses up to 2000 mg/day (175 to 200 mg/kg/day) in a 1-year oral toxicity study. In a second 1-year oral toxicity study, mucoid conjunctivitis was observed at doses of 106 mg/kg/day (1 male and 1 female) and 175 mg/kg/day (1 female), but which was considered to be a species-specific effect. No other compound-related adverse effects were observed at doses up to 2000 mg/day (175 mg/kg/day). The NOAEL for the oral toxicity of mesalamine in dogs was determined to be 175 mg/kg/day.

Carcinogenicity:
Two well-conducted carcinogenicity studies did not reveal evidence of a tumourigenic response in mice or rats, when tested at maximum tolerated dose levels of 2000 and 480 mg/kg/day, respectively.

Genotoxicity:
Mesalamine was negative for genotoxicity in *in vitro* genotoxicity tests, consisting of two bacterial reverse mutation tests, chromosomal aberration tests in Chinese Hamster ovary (CHO) cells and in Chinese Hamster lung fibroblast cells, a mutagenicity assay in *Klebsiella pneumoniae*, sister chromatid exchange assays in human lymphocytes and in CHO cells, and a micronucleus test in human lymphocytes. Mesalamine was also negative for genotoxicity in two *in vivo* mouse erythrocyte micronucleus tests.

Reproductive and Developmental Toxicology:
In a general reproduction study in rats, oral mesalamine doses up to 480 mg/kg/day were given. No effect on fertility, gestation, viability or lactation indices, litter size, pup weight, or pup survival was seen. No mesalamine-related external or internal anomalies were noted in pups at weaning. There were also no effects on the number of viable foetuses or resorptions in dams examined on gestation day (GD) 13.

In embryo-foetal developmental studies in rats and rabbits, animals were given oral mesalamine doses up to 480 mg/kg/day. There were no compound-related effects in the total number of implantation sites, corpora lutea, pre- or post-implantation losses, resorptions, foetal viability indices, and foetal sex distribution. Mean foetal body weights were statistically significantly reduced in rats in the 480 mg/kg/day group, which was a dose that caused maternal toxicity; as such, the decrease in foetal body weights was not considered to represent a direct effect of mesalamine. Similar findings were not observed in rabbits. No compound-related teratogenicity was observed in either species.

The NOAEL for maternal toxicity was determined to be 240 mg/kg/day in rats and 480 mg/kg/day in rabbits. The NOAEL for embryo-foetal developmental toxicity (teratogenicity) was determined to be 480 mg/kg/day in rats and rabbits.

In a peri-/post-natal study in rats, animals were given oral mesalamine at doses up to 480 mg/kg/day on GD 14 through post-partum Day 21. No compound-related effects on gestation, parturition, lactation, or neonatal viability were observed. There were also no mesalamine-related external or internal anomalies observed in pups. The NOAEL for maternal toxicity was determined to be 240 mg/kg/day. The NOAEL for offspring development was considered to be 120 mg/kg/day based on the transient and minor effects on body weight observed at higher doses, which may have reflected maternal toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOCTASA™

Mesalamine Delayed-Release Tablets 800 mg

Read this carefully before you start taking **Octasa** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Octasa**.

Serious Warnings and Precautions

- If you have had a previous reaction to sulfasalazine (e.g. Salazopyrin®):
  - You may get a reaction to Octasa
  - Stop taking Octasa immediately and contact your doctor if you have a reaction
  - See the "To help avoid side effects…." section for symptoms
- Taking Octasa may result in blood problems such as:
  - Low red blood cell count (anemia)
  - Too many white blood cells (eosinophilia, leucocytosis)
  - Low white blood cell count (monocytopenia)

  If this happens and symptoms occur, contact your doctor. See "Other warnings you should know about" section for symptoms.
- Taking Octasa may result in kidney problems. If this happens and symptoms occur, stop taking Octasa and contact your doctor. See "Serious side effects and what to do about them" table for symptoms.
- Taking Octasa may result in lung problems. If this happens and symptoms occur, contact your doctor. See "Serious side effects and what to do about them" table for symptoms.

What is Octasa used for?

Octasa (mesalamine or 5-aminosalicylic acid) is used to treat ulcerative colitis. This is a disease of the large bowel (colon) or back passage (rectum), in which the lining of the bowel becomes inflamed (red and swollen).

How does Octasa work?

Octasa:

- is believed to block the production and action of substances that cause inflamed tissue
- reduces the inflammation (swelling and pain) in these tissues
- has a special coating that protects the tablet until it reaches the bowel

What are the ingredients in Octasa?

Medicinal ingredients: mesalamine

Non-medicinal ingredients: acetone, ferric oxide yellow, ferric oxide red, isopropyl alcohol, lactose monohydrate, macrogol 6000, magnesium stearate, methacrylic acid-methylmethacrylate copolymer (1:2), povidone, sodium starch glycolate (type A), talc and triethylcitrate.

Octasa comes in the following dosage forms:

Octasa 800 mg delayed-release tablets are available for oral administration as coated red/brown oblong tablets.

Do not use Octasa:

- if you are allergic to this drug or to any ingredient in the formulation or component of the container (see What are the ingredients in Octasa?)
- if you are allergic to salicylates (e.g. Aspirin®)
- if you have severe liver problems
- if you have severe kidney problems
- if you have an ulcer (gastric or duodenal)
- if you have a urinary tract blockage or obstruction
- if you are unable to swallow the intact tablet

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Octasa. Talk about any health conditions or problems you may have, including if you:

- have any lung problems including asthma. Lung problems may be worsened by Octasa. Your doctor may monitor your lung function during treatment.
- have liver disease
- have kidney disease. Mesalamine may worsen kidney function or lead to kidney failure. Stop taking Octasa and contact your doctor right away if you experience symptoms. See "Serious side effects and what to do about them" table for symptoms.
- have had a reaction to sulfasalazine in the past. Stop taking Octasa and contact your doctor if you get symptoms such as:
  - stomach pain or cramps
  - fever, severe headache, sore throat or rash
- have ever had a heart-related allergic reaction such as inflammation of the heart muscle or heart sac
- experience worse symptoms of ulcerative colitis, such as:
  - nausea
  - bloody diarrhea
- are pregnant or planning to become pregnant. Octasa may affect your baby.
- breastfeed your baby while taking Octasa. Your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea. Your doctor may advise you to stop breastfeeding your baby.

Other warnings you should know about:

Test for your liver, kidney, blood and lungs

Before and while you are taking Octasa, your doctor may want to monitor your liver, kidneys, blood and lungs to make sure they are all right.

Rarely, blood problems have been reported after using mesalamine products, such as:

- unexplained bruising (without injury)
- bleeding under your skin
- anemia (feeling tired, weak and looking pale, especially on lips, nails and inside of eyelids)
- fever (high temperature)
- sore throat or unusual bleeding (e.g., nose bleeds)

Stop taking Octasa immediately if this occurs. Your doctor may order blood tests before, during or after your treatment.

Octasa contains milk sugar (lactose)

If you are intolerant to lactose, you should note that Octasa contains a small amount of lactose. If you have intolerance to some sugars, contact your doctor before taking this medicine.

Children and adolescents

The safety and effect of Octasa in this age group have not been established.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Octasa:

- drugs that affect the immune system (like azathioprine, or 6-mercaptopurine or thioguanine).
- drugs that prevent the formation of blood clots (like warfarin).

Medical Tests:

Octasa and similar medicines (containing mesalamine) may affect certain test results. If you are about to receive a medical test, tell your doctor that you are taking Octasa.

How to take Octasa:

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Swallow Octasa whole, preferably with some liquid. Do not chew, crush or break the tablets before swallowing them. Octasa may be taken with or without food.

There have been a few reports of intact tablets in the stool. What look like whole tablets may be the remains of the tablet coating. If you observe tablets or tablet shells in the stool, you should consult your doctor.

Usual dose:

Adults (including the elderly)

To treat acute phases of ulcerative colitis your daily dose is 6 tablets once daily or in divided doses.

Overdose:

If you think you, or a person you are caring for, have taken too much Octasa, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose at the right time, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using Octasa?

These are not all the possible side effects you may have when taking Octasa. If you experience any side effects not listed here, tell your healthcare professional.

Organ specific side effects affecting the heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue have been reported.

Common side effects (1% to <10% of patients) seen in clinical studies were:

- ulcerative colitis getting worse
- hemorrhoids
- headache

Uncommon side effects (less than 1% of patients) seen in clinical studies were:

- heart beating too fast or too slow
- upper abdominal pain
- indigestion
- stomach or gut (gastrointestinal) pain
- fever
- muscle pain
- joint pain
- menstrual disorder
- cough
- rosacea (redness in the nose, cheeks, chin and forehead)
- high blood pressure

Side effects seen in post-marketing use:

- sensation of tingling, pricking and numbness
- weakness and pain, usually in hands and feet
- hives
- itching skin
- dizziness
- diarrhea
- stomach pain
- wind (flatulence)
- nausea
- vomiting
- hair loss
- weight loss
- low sperm count (reversible)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Myocarditis/Pericarditis -chest pains or palpitations		✓	
VERY RARE			
Hepatitis -flu-like symptoms -yellowing of the skin and eyes		✓	
Pancreatitis -pain in upper abdomen and back -feeling sick		✓	
Lung disease -allergic reaction causing difficulty in breathing, wheezing and a build-up of fluid in the lungs -pneumonia -swelling of the lining around the lungs and the breast cavity (pleurisy)			✓
Kidney problems -changes in urine output -cloudy or tea coloured urine -blood in your urine -weight gain (from retaining fluid) -confusion -swelling of the eyes, hands, legs and feet -other less specific symptoms may include: drowsiness, fatigue, nausea, vomiting, rash, persistent itching, and back pain			✓
Blood problems -severe decrease in blood cells that can cause weakness, bruising or increase the chance of infections -low blood cell counts -decrease in blood platelets which increases the risk of bleeding			✓
Allergic reactions -rash or skin eruption			✓
Drug fever -fever that occurs while taking the medicine and goes away when the medicine is stopped		✓	
NOT KNOWN			
Disorder of the immune system -Lupus-like syndrome which can cause swelling of the heart sac or membranes		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
around the lungs and heart, rash and/or joint pain			
Intolerance reactions -increase of symptoms of the underlying disease			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not store above 25°C. Store in the original package.

Keep out of reach and sight of children.

If you want more information about Octasa:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html).

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