CLAVERSAL

SmPC OF CLAVERSAL 500 mg Tablets, CLAVERSAL 500 mg Suppositories, CLAVERSAL Rectal Foam

1. NAME OF THE MEDICINAL PRODUCT

Claversal 500 mg gastro-resistant Tablets
Claversal 500 mg Suppositories
Claversal 1g Rectal Foam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Claversal contains 500 mg of mesazaline.(*)
Excipients: 2.13 mmol of sodium (49 mg) and others excipients.

Each suppository of Claversal contains 500 mg of mesazaline.(*)

Each application (5 g of foam) of Claversal rectal foam contains 1 g of mesalazine.(*)
Excipients:1.36g Glycerol(E-422), 0.011g methyl parahydroxybenzoate (E-218), 0.002g propyl parahydroxybenzoate (E-216), 0.014g sodium methabisulphate (E-223) and others excipients

(*) Mesalazine is 5-aminosalicylic acid (5-ASA).

3. PHARMACEUTICAL FORM

Claversal is supplied in gastro-resistant tablets, suppositories and foam for rectal administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Claversal tablets are indicated in:
    - Treatment of the acute phase of mild or moderate ulcerative colitis.
    - Maintenance treatment of remission in ulcerative colitis (including patients unable to tolerate salazosulphapyridine).
    - Treatment of the acute phase of Crohn's disease and maintenance of the remission of Crohn's disease.

- Claversal suppositories are indicated for the treatment of the acute phase of distal ulcerative colitis (proctitis and proctosigmoiditis) and for the maintenance treatment of remission of distal ulcerative colitis (proctitis and proctosigmoiditis).
- Claversal Rectal Foam is indicated for the treatment of distal ulcerative colitis.

4.2 Posology and method of administration

During the acute inflammatory phase and in long-term maintenance therapy, the patient must accurately follow the treatment established by the doctor to ensure the intended therapeutic effect.

The dosage should be adjusted according to patient response. The following dosage is recommended:

Adults

Claversal 500 mg Tablets
One tablet every 8 hours. The tablets must be administered before meals and must be taken whole with some fluid.

Claversal 500 mg Suppositories
Up to 3 suppositories a day, in three different doses, the last administered at bedtime.

Claversal Rectal Foam
In case of rectosigmoid involvement, the recommended dose is 1 g (1 application) a day for 4 to 6 weeks.

If the disease affects the descending colon, 2 g (2 applications of 1 g) once a day for 4 to 6 weeks is recommended.

Elderly

Administration of Claversal in the elderly must be performed with caution and always limited to patients with normal renal function.

Children

The efficacy and safety of use of Claversal have not been established in children under 5 years of age.

METHOD OF ADMINISTRATION

Claversal Rectal Foam

Read the instructions carefully before using Claversal Rectal Foam for the first time.

1. Mix the content by shaking vigorously for about five seconds.
2. Before the first dose, remove the safety strap from under the dosing head.
3. Connect the applicator firmly into the aerosol discharge tube and align the notch placed under the dosing head with the discharge tube.
4. Hold the package upside-down over the palm of the hand, with the index finger over the dosing head (the product can be only dispensed when the aerosol is upside down with the filling head downwards).
5. The easiest way to use the aerosol is to raise one foot onto a smooth area such as a chair or stool, and insert the applicator into the rectum. A lubricant solution can be applied onto the end of the applicator for greater comfort.
6. To administer one dose, fully press the dosing head once and release it. To administer a second dose, press and release the dosing head again. Wait for at least 15 seconds before removing the applicator.

Note: the aerosol only works when it is held with the dosing head downwards.

4.3 Contraindications

Claversal must not be administered in the following cases:

- History of hypersensitivity to salicylates.
- Duodenal or gastric ulcer
- Bleeding diathesis.

4.4 Special warnings and special precautions for use

Administration of Claversal must be performed with caution in the following cases:

- Patients with severe liver or renal insufficiency. As 5-ASA is cleared mainly by acetylation and subsequent urinary excretion, patients with impaired liver function or renal failure should be closely monitored, so it is advisable to perform liver and renal function tests before instituting treatment and regularly during it.
- Patients with a history of hypersensitivity to sulfasalazine; though in general it appears that hypersensitivity reactions to mesalazine are less common than those seen with sulfasalazine.

Claversal tablets must not be administered concomitantly with laxatives such as lactulose or similar, as this reduces the pH of faeces and can impede drug substance release.

Warnings about excipients

Claversal tablets contains 2.13 mmol (49g) of sodium per tablet, which should be taken into account in the treatment of patients with low-sodium diets.

Claversal Rectal Foam contains sodium metabisulphite, that can cause allergic reactions, including anaphylactic reactions and bronchospasm in susceptible patients, particularly those with a history of asthma or allergy.

Claversal Rectal Foam contains methyl and prophyl parahydroxybenzoate (parabens) that can cause hives. They can generally cause late reactions such as contact dermatitis. Immediate reactions with hives and bronchospasm are rare.

4.5 Interaction with other medicinal products and other forms of interaction

As occurs with other salicylates, mesalazine can:

- Enhance the effect of coumarin anticoagulants
- Enhance the blood sugar level reducing effect of sulphonylureas
- Antagonise the uricosuric effects of probenecid and sulphynpyrone.
- Evidence toxicity of salicylates at doses lower than usual when administered concomitantly with furosemide due to the competition for renal excretion sites.
- Reduce the natriuretic effect of spironolactone.

Mesalazine can delay methotrexate excretion.

Laxatives such as lactulose or similar can prevent mesalazine release from the tablet thereby reducing its effect (see Section 4.4. Special warnings and special precautions for use).

4.6 Pregnancy and lactation

No adequate data are available on the use of Claversal during pregnancy or lactation. As mesalazine is a salicylate, its use is not recommended during pregnancy or lactation, unless the benefit of treatment outweighs the possible risks.

4.7 Effects on the ability to drive and use machines

There is no evidence that Claversal has an effect on the ability to drive cars or use machines.

4.8 Adverse reactions

In clinical trials performed with enema in mesalazine foam, the most common adverse events (frequency > 5%) were swelling and abdominal pain.

The adverse reactions reported with mesalazine are listed below, classified by organs or systems and frequencies. The frequencies are defined as follows: common > 1%, rare <1 per 1000 and very rare < 1 per 10,000.

The following adverse reactions have been described on rare occasions:

Gastrointestinal system: nausea, abdominal pain, diarrhoea, pancreatitis.
Central nervous system: headache, neuropathy.
Skin and appendages: reddening (including itching and hives), local irritation (rectal forms).
Urinary tract system: renal disorders, acute and chronic interstitial nephritis, renal failure.
Hepatobiliary: transient liver enzyme increases, hepatitis.
Haematological effects: leukopenia, neutropenia, thrombocytopenia, aplastic anaemia.
Hypersensitivity reactions, including pulmonary and heart changes: fever, myalgia, arthralgia, alveolitis, myocarditis, pericarditis.

Exacerbation of colitis symptoms is very rare.

4.9 Overdose

No cases of overdose have been described to date for rectal preparations. In case of massive intake of tablets, the treatment includes gastric lavage, inducing vomiting, together with symptom and support measures. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mesalazine belongs to the pharmacotherapeutic and ATC group A07C

Mesalazine is one of the two components of sulfasalazine, the other being sulphapyridine. While mesalazine is the active fraction, sulphapyridine is responsible for most adverse events associated with therapy with sulfasalazine.

<u>Mechanism of action</u>

Although the anti-inflammatory mechanism of action of 5-ASA is unknown, several possibilities are considered:

- Inhibition of prostaglandin synthesis (cyclooxygenase inhibition pathway), reducing inflammatory prostaglandin output.
- Inhibition of chemotactic leukotriene synthesis (lipooxygenase inhibition pathway), therefore reducing inflammation.
- Inhibition of chemotaxis of macrophages and neutrophils in the swollen tissue.

The most recent data suggest that 5-ASA is a biological antioxidant and its activity is based on the uptake of oxygen free radicals. In this activity, 5-ASA differs from sulfasalazine, sulphapyridine, N-acetyl-5-ASA (Ac-5-ASA) and other salicylates.

5.2 Pharmacokinetic properties

Absorption

Oral administration. After the administration of oral doses of 500 mg of mesalazine t.i.d. to patients with ulcerative colitis or Crohn's disease, the steady-state mean plasma concentrations of 5-ASA and Ac-5-ASA (major metabolite) are 0.7µg/ml and 1.2 µg/ml, respectively. The peak plasma levels with the retard release forms are obtained at 5 hours post-administration. Recovery (at the highest dose) in urine (44%) and faeces (35%) shows that 5-ASA is available for its local and systemic action. In fasting healthy subjects, the peak plasma concentration of 1.3 µg/ml and 2.3 µg/ml of 5-ASA and Ac-5-ASA respectively was obtained at 6 hours post-administration.

Rectal administration of the suppositories. Administration of mesalazine 500 mg t.i.d. suppositories to patients with ulcerative colitis causes steady plasma concentrations of 5-ASA and Ac-5-ASA of 0.10 µg/ml and 0.50 µg/ml, respectively. Systemic availability, measured on the basis of urinary recovery, accounts for 13%. A low systemic availability has been seen, 10.8%, in healthy subjects administered mesalazine 500 mg suppositories.

Administration of the rectal foam. Claversal Rectal Foam is designed to release mesalazine directly at the proposed site of action, i.e., colon and rectum, with low systemic exposure levels. Approximately 0.8% of the dose administered is cleared in urine and the rest in faeces. After rectal administration of 2 g the mean plasma concentrations for 5-ASA and Ac-5-ASA were 1.3 µg/ml and 2.3 µg/ml respectively. The elimination half-life for absorbed fraction of mesalazine is about 5 hours. The studies performed show that approximately 27% of the dose of 2 g had dispersed to the descending colon four hours after rectal administration.

Acetylation

Acetylation of 5-ASA occurs in the liver and the colon wall, regardless of the acetylator status. It appears that the acetylation process is saturable; however, at therapeutic doses (250-500 mg) neither the peak plasma concentration nor the area under the curve of plasma concentration vs. time for 5-ASA evidenced any deviation from linearity of the dose in the steady state.

Clearance

After oral administration, 5-ASA is cleared at a high percentage as Ac-5-ASA both in urine and in faeces. In fact, over 90% of the drug identified in urine is in metabolite form. After rectal administration, 5-ASA is cleared mainly unchanged in faeces.

5.3 Preclinical safety data

Preclinical data based on conventional pharmacology, repeated-dose toxicology, genotoxicity, carcinogenicity and reproduction studies have not shown any special risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Claversal 500 mg Tablets.

Anhydre sodium carbonate, glycine, povidone K30, microcrystalline cellulose, carboxymethyl sodium starch, colloidal silica oxide, calcium stearate, methacrylic acid polymer (Eudragit L and Eudragit S), micronised talc, titanium dioxide, macrogol 6000, yellow iron oxide, red iron oxide, isopropyl alcohol.

Claversal 500 mg Suppositories Solid fat (Witepsol 45).

Claversal Rectal Foam Mono sorbitan oleate, polysorbate 20, emulsifying wax, colloidal anhydrous silica, sodium methabisulphate, disodium edetate, methyl parahydroxybenzoate, propyl parahydroxybenzoate, dodecahydrated sodium phosphate hydrogen, dihydrate sodium phosphate dihydrogen, glycerine, macrogol 300, purified water, propane, iso-butane, and n-butane.

6.2 Incompatibilities

None described.

6.3 Shelf life

Claversal 500 mg Tablets: Two years.
Claversal 500 mg Suppositories: 12 months.
Claversal Rectal Foam: Three years.

6.4 Special precautions for storage

Claversal 500 mg Tablets.

Claversal Tablets must not be stored at temperatures above 25ºC.

Claversal 500 mg Suppositories.

Claversal suppositories must not be stored at temperatures above 25ºC, must be protected from light and kept in the original package.

Claversal 1g Rectal Foam.

Do not store at temperatures above 30ºC. Claversal rectal foam is supplied in a pressurised package containing a flammable propellant. It must be kept away from any source of heat, flames or ashes, including cigarettes. It must be protected from direct sunlight and must not be disposed of or burnt, not even when empty.

6.5 Nature and contents of container

Claversal 500 mg Tablets.

Package containing 100 tablets, oblong (capsular form), salmon-coloured,

Claversal 500 mg Suppositories.

White PVC/PE blister containing 100 opaque beige suppositories.

Claversal Rectal Foam.

Aerosol package of one cylindrical piece, white, fitted with a 5 ml dosing valve.

Each aerosol delivers 14 applications An overage of about 21% is included in the filling weight to ensure that the last application is released adequately

The package also contains 14 disposable applicators and 14 disposable plastic bags

6.6. Special precautions for disposal

Claversal Rectal Foam

Separate the applicator and dispose of it using one of the accompanying plastic bags.

7. HOLDER OF THE marketing authorisation

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8. MARKETING AUTHORIZATION NUMBER(S)

Claversal 500 mg Tablets	58.101
Claversal 500 mg Suppositories	60.607
Claversal 1g Rectal Foam	61.335

9. DATE OF FIRST AUTHORISATION

Claversal 500 mg Tablets	20-12-1988
Claversal 500 mg Suppositories	31-07-1995
Claversal 1g Rectal Foam	31-03-1997

10. DATE OF REVISION OF THE TEXT

June, 2009.