

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Macrolief 13.125g + 351mg + 179mg + 47mg sachet, powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains the following quantitative composition of active ingredients:

| | |
|---------------------------|----------|
| Macrogol 3350 | 13.125 g |
| Sodium Chloride | 0.3507 g |
| Sodium Hydrogen Carbonate | 0.1785 g |
| Potassium Chloride | 0.0466 g |

The content of electrolyte ions per sachet following reconstitution in 125 ml of water is equivalent to:

| | |
|----------------------------------|-----------|
| Sodium | 65 mmol/l |
| Chloride | 53 mmol/l |
| Hydrogen Carbonate (Bicarbonate) | 17 mmol/l |
| Potassium | 5 mmol/l |

Excipient(s) with known effect:

- Sorbitol (E420)
- Sodium (8.1 mmol (187 mg) per sachet)
- Potassium (0.63 mmol (25 mg) per sachet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution
Single-dose sachet containing a free flowing white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of chronic constipation. Macrolief is also effective in resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon.

4.2 Posology and method of administration

Posology

Chronic Constipation:

A course of treatment for chronic constipation with Macrolief does not normally exceed 2 weeks, although this can be repeated if required.

As for all laxatives, prolonged use is not usually recommended. Extended use may be necessary in the care of patients with severe chronic or resistant constipation, secondary to multiple sclerosis or Parkinson's Disease, or induced by regular constipating medication in particular opioids and antimuscarinics.

Adults, adolescents and the elderly: 1-3 sachets daily in divided doses, according to individual response. For extended

use, the dose can be adjusted down to 1 or 2 sachets daily.

Children below 12 years old: Not recommended.

Faecal Impaction:

A course of treatment for faecal impaction with Macrolief does not normally exceed 3 days.

Adults, adolescents and the elderly: 8 sachets daily, all of which should be consumed within a 6 hour period.

Children below 12 years old: Not recommended.

Patients with impaired cardiovascular function: For the treatment of faecal impaction the dose should be divided so that no more than two sachets are taken in any one hour.

Patients with renal insufficiency: No dosage change is necessary for the treatment of constipation or faecal impaction.

Method of administration

Each sachet should be dissolved in 125 ml water. For use in faecal impaction, 8 sachets may be dissolved in 1 litre of water.

4.3 Contraindications

Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease and ulcerative colitis and toxic megacolon.

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The fluid content of Macrolief when re-constituted with water does not replace regular fluid intake and adequate fluid intake must be maintained.

Diagnosis of impaction/faecal loading of the rectum should be confirmed by physical or radiological examination of the rectum and abdomen.

Mild adverse drug reactions are possible as indicated in Section 4.8. If patients develop any symptoms indicating shifts of fluids/electrolytes (e.g. oedema, shortness of breath, increasing fatigue, dehydration, cardiac failure) Macrolief should be stopped immediately and electrolytes measured, and any abnormality should be treated appropriately.

The absorption of other medicinal products could transiently be reduced due to an increase in gastro-intestinal transit rate induced by Macrolief (see section 4.5).

Paediatric population

Not recommended.

Special information about some of the ingredients

Macrolief contains 0.63 mmol (25 mg) of potassium per sachet. This should be taken into consideration when more than one sachet daily is taken by patients with reduced kidney function or patients on a controlled potassium diet.

Macrolief contains 8.1 mmol (187 mg) of sodium per sachet which should be taken into consideration by patients on a controlled sodium diet.

The lemon lime flavour in Macrolief contains sorbitol (E420).

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Macrogol 3350 raises the solubility of medicinal products that are soluble in alcohol and relatively insoluble in water. There is a possibility that the absorption of other medicinal products could be transiently reduced during use with Macrolief (see section 4.4).

There have been isolated reports of decreased efficacy with some concomitantly administered medicinal products, e.g. anti-epileptics. Therefore, other medicines should not be taken orally for one hour before and for one hour after taking Macrolief.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of macrogol 3350 in pregnant women. Studies in animals have shown indirect reproductive toxicity (see Section 5.3). Clinically, no effects during pregnancy are anticipated, since systemic exposure to macrogol 3350 is negligible.

Macrolief can be used during pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to macrogol 3350 is negligible.

Macrolief can be used during breast-feeding.

Fertility

There are no data on the effects of macrogol 3350 on fertility in humans. There were no effects on fertility in studies in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Macrolief has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Reactions related to the gastrointestinal tract occur most commonly.

These reactions may occur as a consequence of expansion of the contents of the gastrointestinal tract, and an increase in motility due to the pharmacologic effects of Macrolief. Mild diarrhoea usually responds to dose reduction.

List of adverse reactions

The frequency of the adverse effects is not known as it cannot be estimated from the available data.

| | |
|---|---|
| <i>Immune system disorders</i> | Allergic reactions, including anaphylactic reactions, dyspnoea and skin reactions.(see below) |
| <i>Skin and subcutaneous tissue disorders</i> | Allergic skin reactions including angioedema, urticarial, pruritus, rash, erythema. |
| <i>Metabolism and nutrition disorders</i> | Electrolyte disturbances, particularly hyperkalaemia and hypokalaemia. |
| <i>Nervous system disorders</i> | Headache |
| <i>Gastrointestinal</i> | Abdominal pain, diarrhoea, vomiting, nausea, |

| | |
|---|---|
| <i>disorders</i> | dyspepsia, abdominal distension, borborygmi, flatulence and anorectal discomfort. |
| <i>General disorders and administration site conditions</i> | Peripheral oedema |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Severe distension or pain can be treated by nasogastric aspiration. Extensive fluid loss by vomiting or diarrhoea may require correction of electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxatives.

ATC code: A06A D65

Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defaecation. Electrolytes combined with macrogol 3350 are exchanged across the intestinal barrier (mucosa) with serum electrolytes and excreted in faecal water without net gain or loss of sodium, potassium and water.

Comparative studies in faecal impaction using active controls (e.g. enemas) have not been performed. However, results from a non-comparative study have shown that, from a population of 27 adult patients, the listed combination of medicinal products cleared faecal impaction in 12/27 (44%) patients after one day's treatment, increasing to 23/27 (85%) following two days' treatment and 24/27 (89%) recovered at the end of three days.

Clinical studies using the listed medicinal products for the treatment of chronic constipation have shown that the dose required to produce normally formed stools tends to decrease over time. Many patients respond to between one and two sachets a day, but this dose should be adjusted depending on individual response.

5.2 Pharmacokinetic properties

Macrogol 3350 is unchanged along the gut. It is virtually unabsorbed from the gastro-intestinal tract and. Any macrogol 3350 that is absorbed is excreted via the urine.

5.3 Preclinical safety data

Preclinical studies provide evidence that macrogol 3350 has no significant systemic toxicity potential, based on conventional studies of pharmacology, repeated dose toxicity and genotoxicity.

There were no direct embryotoxic or teratogenic effects in rats even at maternally toxic levels that are a multiple of 66 x the maximum recommended dose in humans for chronic constipation and 25 x for faecal impaction. Indirect embryofetal effects, including reduction in fetal and placental weights, reduced fetal viability, increased limb and paw

hyperflexion and abortions, were noted in the rabbit at a maternally toxic dose that was 3.3 x the maximum recommended dose in humans for treatment of chronic constipation and 1.3 x for faecal impaction. Rabbits are a sensitive animal test species to the effects of GI-acting substances and the studies were conducted under exaggerated conditions with high dose volumes administered, which are not clinically relevant. The findings may have been a consequence of an indirect effect of macrogol 3350 related to poor maternal condition as the result of an exaggerated pharmacodynamic response in the rabbit. There was no indication of a teratogenic effect.

There are long-term animal toxicity and carcinogenicity studies involving macrogol 3350. Results from these and other toxicity studies using high levels of orally administered high molecular weight macrogols provide evidence of safety at the recommended therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Saccharin sodium

Orange flavour

(Orange flavour contains: flavouring substances and flavouring preparations, maltodextrin, acacia gum (E 414), alpha-tocopherol (E 307))

Lemon-lime flavour

(Lemon-lime flavour contains: natural lemon oil, natural powder flavour lemon, powder flavour lime, maltodextrin, mannitol (E 421), gluconolactone (E 575), sorbitol (E420), acacia gum (E 414), colloidal anhydrous silica (E 551))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

Reconstituted solution: 24 hours

6.4 Special precautions for storage

Sachet: Do not store above 25 °C.

Reconstituted solution: Store covered in a refrigerator (2 °C to 8 °C).

6.5 Nature and contents of container

The sachet is composed of paper, ethylene / methacrylic acid co-polymer and aluminium.

Sachets with 13.8 g of powder are packed in cartons of 2, 6, 8, 10, 20, 30, 50, 60 (2x30) and 100 (2x50).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

After twenty-four hours, any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.

Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/224/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th July 2013

10 DATE OF REVISION OF THE TEXT

August 2016