

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Macrosoft 10 g Powder for Oral Solution in Sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 10 g macrogol 4000.

Excipient with known effect:

Each sachet contains 0.2 mg sorbitol (contained in lemon-grapefruit flavour).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution in sachet.

White powder, free of large agglomerates, with an odour and taste of lemon, packed in a sachet for the preparation of an oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of constipation in adults and children aged 8 years and above.

An organic disorder should have been ruled out before initiation of treatment with Macrosoft. Macrosoft should remain a temporary adjuvant treatment to appropriate lifestyle and dietary management of constipation, with a maximum 3-months treatment course in children. If symptoms persist despite associated dietary measures, an underlying cause should be suspected and treated.

4.2 Posology and method of administration

Posology

It is generally recommended to consider healthy lifestyle measures such as adequate hydration, physical activity, and increased natural fibre intake. In case the symptoms persist or get worse, a physician should be consulted.

Adults

1 to 2 sachets (10 to 20 g macrogol 4000) per day, preferably taken as a single dose in the morning.

Paediatric population

~ **Children ≥ 8 years and adolescents:** 1 to 2 sachets (10 to 20 g macrogol 4000) per day, preferably taken as a single dose in the morning.

~ **Children (<8 years):** Macrosoft is not recommended for use in children below the age of 8 years.

The daily dose should be adapted as required to produce regular soft stools and may range from one sachet every other day (especially in children) up to 2 sachets a day. If administered regularly, the frequency of bowel movements tends to be one movement per day. In children, treatment should not exceed 3 months due to a lack of clinical data for treatment lasting longer than 3 months. Treatment-induced restoration of bowel movements will be maintained by lifestyle and dietary measures.

Method of administration

Oral use.

1 to 2 sachets per day, preferably taken as a single dose in the morning. The content of each sachet should be dissolved in a glass of water just before use. The effect of Macrosoft becomes apparent within 24 to 48 hours after its administration. The reconstituted solution is colourless & clear.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe inflammatory bowel disease (such as ulcerative colitis, Crohn's disease) or toxic megacolon
- Digestive perforation or risk of digestive perforation
- Ileus or suspicion of intestinal obstruction or symptomatic stenosis
- Painful abdominal syndromes of indeterminate cause

4.4 Special warnings and precautions for use

As with all laxatives, an organic disorder should have been ruled out before initiation of treatment. Without investigating the cause of constipation, Macrosoft should not be taken on a continuous daily basis for an extended period of time. The patient is instructed to seek medical advice in case of persistent abdominal pain.

In case of diarrhoea, caution should be exercised in patients who are prone to a disturbance of water or electrolyte balance (e.g. elderly, patients with impaired hepatic or renal function or patients taking diuretics) and electrolyte control should be considered.

Allergic conditions (such as anaphylactic shock, anaphylactic reaction, angioedema, urticaria, rash and hypersensitivity) have been reported with drugs containing macrogol (polyethylene glycol).

Macrosoft contains sorbitol. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Macrogol 4000 increases the osmotic pressure in the gut, and thus might modify the intestinal absorption of drugs concomitantly administered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Non-clinical studies are insufficient with respect to reproductive toxicity. No effects during pregnancy are anticipated, since systemic exposure to macrogol 4000 is negligible. Macrosoft can be used during pregnancy

Breast-feeding

There are no data on the excretion of macrogol 4000 in breast milk. No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to macrogol 4000 is negligible (see section 5.2). Macrosoft can be used during breast-feeding

Fertility

No studies on the effect on human fertility have been conducted. No effects on fertility are anticipated, since systemic exposure to macrogol 4000 is negligible. (see section 5.2).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Undesirable effects are listed under headings of frequency using the following conventions:
Very common: $\geq 1/10$, Common: $\geq 1/100$ to $< 1/10$, Uncommon: $\geq 1/1,000$ to $< 1/100$, Rare: $\geq 1/10,000$ to $< 1/1,000$, Very rare: $< 1/10,000$, Not known: cannot be estimated from the available data

Tabulated list of adverse reactions

Adult population:
Generally, adverse reactions have been minor and transitory and have mainly concerned the gastrointestinal system.

System Organ Class	Adverse Drug Reaction
Immune system disorders	<u>Not known:</u> anaphylactic shock, anaphylactic reaction, angioedema, urticaria, rash and hypersensitivity
Gastro- intestinal disorders	<u>Common:</u> diarrhoea, abdominal pain, abdominal distension, nausea <u>Uncommon:</u> vomiting, faecal incontinence <u>Not known:</u> flatulence

Paediatric population
As in adult population, adverse reactions have generally been minor and transitory and have mainly concerned the gastrointestinal system. The publications that were considered for the list of undesirable effects included children from 6 months to 18 years of age.
Frequency type and severity of adverse reactions in children have been observed to be comparable to adults.

System Organ Class	Adverse Drug Reaction
Immune system disorders	<u>Not known:</u> anaphylactic shock, anaphylactic reaction, angioedema, urticaria, rash and hypersensitivity
Gastro- intestinal disorders	<u>Common:</u> diarrhoea, abdominal pain <u>Uncommon:</u> abdominal distension, vomiting, nausea <u>Not known:</u> flatulence

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

Symptoms
Overdose and/or abuse may lead to diarrhoea, abdominal pain, abdominal distention and vomiting which disappears when treatment is temporarily interrupted or the dose reduced.

Management
Excessive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for constipation, osmotically acting laxatives, ATC code: A06AD15

Mechanism of action

Macrogol 4000 softens the stool by retaining water molecules. Thereby it increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools which facilitates defaecation.

Pharmacodynamic effects

Different doses of macrogol are shown to have different effects on intestinal function. In normal volunteers, low doses increase stool weight without modifying oro-anal transit time. In constipated patients, low doses decrease stool consistency, increase stool frequency, and facilitate stool evacuation without modifying stool weight and colonic transit time. Bloating produced by the administration of macrogol is usually due to intestinal distention by water binding.

Clinical efficacy

Adult population:

A multicentre, double-blind, randomised, parallel-group 4 weeks study involving 266 patients with idiopathic chronic constipation compared the efficacy and tolerability of two different doses of macrogol 4000 (10 or 20 g) with two different doses of macrogol 3350 plus electrolytes (5.9 or 11.8 g). The results showed that both doses of macrogol 4000 and macrogol 3350 were effective in treating the symptoms of constipation and were well tolerated. The treatment improved stool consistency in all groups from baseline, with the percentage of patients with normal stool consistency increasing during the course of the study. During the course of the study straining at stool, rectal evacuation, abdominal bloatedness and abdominal pain were all significantly improved. Similarly, the quality of life was significantly improved compared with baseline. Most patients ($\geq 67.3\%$) had their first stool within 1 day of starting treatment.

Paediatric population:

Macrogol 4000 was used to treat constipation in a 3-month multicentre non-comparative study with 96 children aged from 6 months - 15 years. The study confirmed the efficacy and wide safety margin of PEG 4000 also in diet-resistant constipation. More than 90% of children recovered normal bowel habits, with an improvement in stool frequency, consistency, appetite, fecal soiling, fecal mass in the rectum, and abdominal pain related to constipation. For children aged 8 years to 15 years the study found a median effective dose comparable to the daily dosage for the treatment of constipation in adults (i.e., 10–20 g). A pooled Cochrane analysis suggested that macrogol preparations might be superior to placebo, lactulose, and milk of magnesia in terms of stool amounts generated for the treatment of childhood constipation.

5.2 Pharmacokinetic properties

Absorption

Macrogol 4000 is only minimally absorbed, i.e. 0.05%, from the intestine of healthy subjects following an oral administration of 2 g.

Metabolism

Like other polyethylene glycols with molecular masses exceeding 3000 Da, macrogol 4000 does not undergo any intestinal enzymatic degradation or bacterial metabolism.

Elimination

Macrogol 4000 is eliminated in the faeces with very high recovery rates ranging between 93% and 100%. Urinary excretion of macrogols occurs through passive glomerular filtration. Macrogol 4000 is excreted unchanged in urine with mean urinary recovery ranging from 0.05% to 0.46%.

5.3 Preclinical safety data

Toxicological studies in different species of animals did not reveal any signs of systemic or local gastrointestinal toxicity of macrogol 4000. Macrogol 4000 had no teratogenic, mutagenic, nor carcinogenic effect. No studies on

fertility are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium citrate, anhydrous
 Citric acid, anhydrous
 Calcium citrate
 Acesulfame K
 Potassium chloride (with 0.9% silica colloidal, anhydrous)
 Lemon-grapefruit flavour (contains natural lemon oil, liquid flavour grapefruit, powder flavour maracuja, powder flavour grenadine/raspberry, mannitol (E421), gluconolactone (E575), sorbitol (E420), anhydrous silica colloidal (E551))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
 Store in its original container to protect from light.

6.5 Nature and contents of container

Sachet (Aluminium / Paper)
 Unidose sachets in packs of 10 or 20 sachets.
 Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
 The reconstituted solution is colourless & clear.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd
 T/A SANOFI
 Citywest Business Campus
 Dublin 24
 Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/192/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th January 2015.

10 DATE OF REVISION OF THE TEXT

August 2017