

MACROGOL 4000

 **MACRO-RE ADULTS**

Packaging: 4 microenemas of 9g
6 microenemas of 9g

 **MACRO-RE BABY**

Packaging: 4 microenemas of 6 g

 **MACRO-RE ENEMA**

Packaging: 2 enemas of 120 ml
10 enemas of 120 ml



Treatment of constipation and colon cleanser



Components

Macrogol 4000 is an inert, biologically inactive, high-molecular-weight ethylene glycol polymer with an approximate mean molecular weight of 4000 g/mol.

It exerts its laxative action by increasing the water content of stools due to its ability to interact with water molecules.



How to use

Microenemas for the treatment of constipation.

Macro-re Adults:

4 microenemas of 9g

6 microenemas of 9g

Macro-re Baby:

4 microenemas of 6 g

For adults and children children:

1 micro-enema when needed or according to doctor's opinion.



How to use

The execution of the enema is a procedure aimed at intestinal washing in cases of intestinal irregularities or in cases of preparation for surgery or particular diagnostic investigations.

Macro-re enema:

2 enemas of 120 ml
10 enemas of 120 ml



Pre-Clinical

- Two formulations of PEG 4000 in micro-enemas have shown in mice higher **evacuating efficacy** than glycerol and more importantly evacuating activity only in acute (within 60 minutes from administration) and no further activity in the following 24 hours.
- This important finding confirms no systemic activity of PEG 4000 when administered via enema.



Pre-Clinical

- In 2019 Macro-re Adults and Macro-re Baby were sent to a preclinical study by the **Federico II Pharmacology group** to evaluate its safety and efficacy.
- A new formulation of PEG 4000 in micro-enemas and a second formulation of PEG suppositories have been studied in two groups
- The micro-enemas have shown to be **more efficacious than suppositories** in the more severe cases with combined better control in cases of associated hemorrhoidal syndrome.

No adverse events have been reported during the treatment or the follow-up period.

Clinical case



Emanuele Salvatore Aragona
 Centro di Medicina Rigenerativa; Pronto Soccorso Emergenza Urgenza
 Humanitas Mater Domini – Castellanza (Varese)

L'utilizzo di macrogol per via rettale nel trattamento della stipsi e costipazione intestinale in medicina d'urgenza nei pazienti anziani o politrattati

In the post covid-19 period, the Humanitas center organized a small spontaneous study with Enemas based on PEG 4000 and PEG 400 to treat patients who came to the emergency room with occlusive or semi-occlusive clinical situation. The comparison group was treated with sodium phosphate-based enemas. In patients treated with PEG 400/4000 enemas was noted:

- Better compliance
- Significantly better performance
- Digitoclasia of feces in ampoule much easier
- Much more modest inflammatory phenomena affecting the mucous membranes

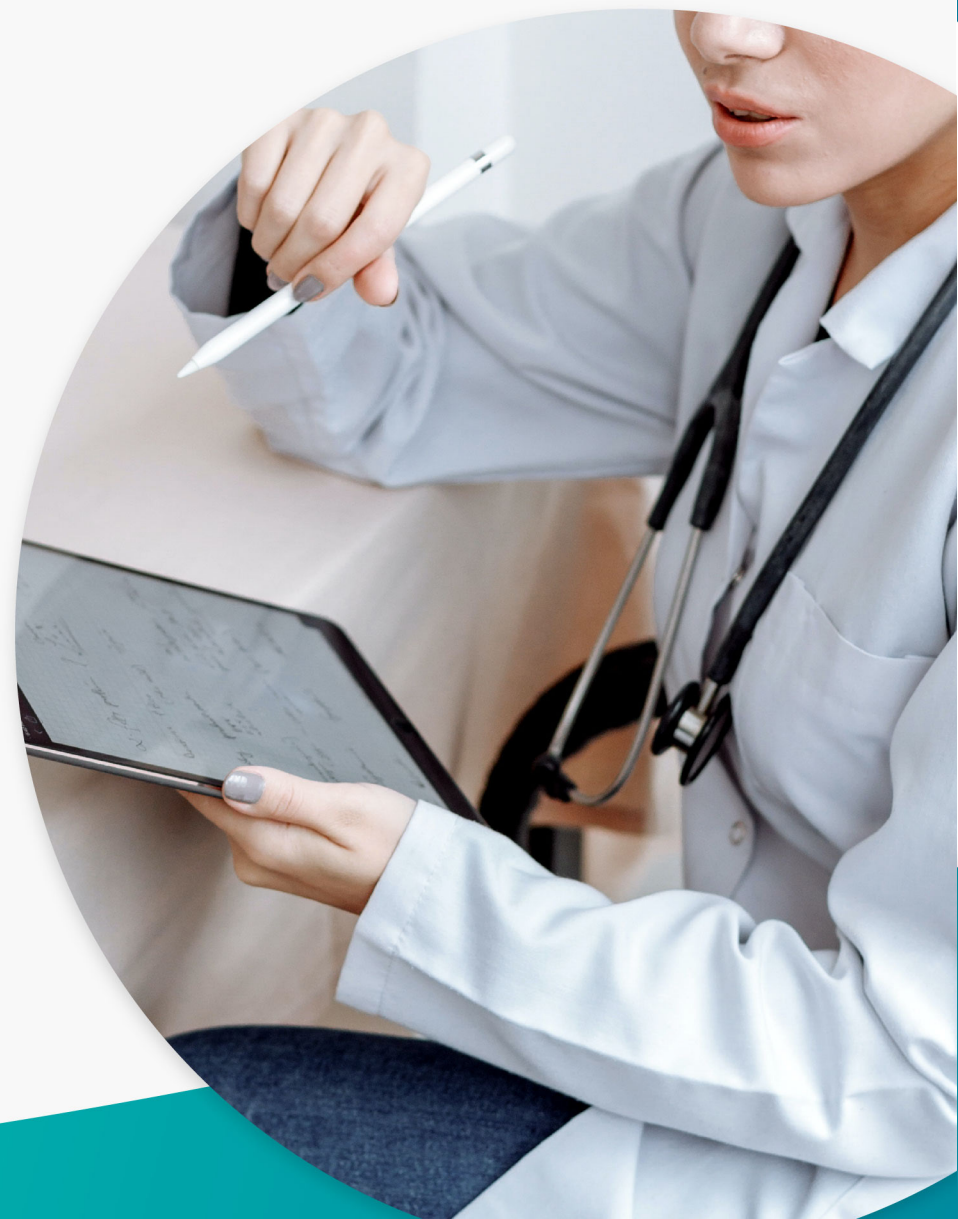
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Pazienti con stipsi	Pazienti con fecaloma	Ragade anale	Compliance dopo clistere	Efficacia e tolleranza	Danni mucosali assenza	Pulizia intestinale efficacia	Costipazione residua
60%	45%	10%	90%	90%	80%	100%	0%

Paediatric Trial

A new formulation of PEG 4000 in micro-enemas has been studied in 90 pediatric cases for constipation.

- 73 of them have had **full normalization** of the symptoms with a mean evacuation time after administration of 35 ± 15.4 minutes.
- Given the good results obtained with this observational study, the use of micro-enemas of PEG4000 given rectally has shown to be efficacious in the **children constipation management**.



NICENational Institute for
Health and Care Excellence

Paediatric Trial

Offer the following oral medication regimen for disimpaction if indicated:

- Polyethylene glycol, using an escalating dose regimen as the first-line treatment.
- Add a stimulant laxative if polyethylene glycol does not work.
- Substitute a stimulant laxative if polyethylene glycol is not tolerated by the child or young person. Add another laxative such as lactulose or docusate if stools are hard.

NICE guidelines for disimpaction in children PEG used as a first-line therapy for the management of dis-impaction in children.



Paediatric Trial

**Evaluation and Treatment of Functional Constipation in
Infants and Children: Evidence-Based Recommendations
from ESPGHAN and NASPGHAN**

*M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Laungendam, S.
Nurko, A. Staiano, Y. Vandenplas, and M.A. Benninga*

Paediatric Trial

Medication Recommendations for fecal disimpaction

First line treatment: oral PEG, with or without electrolytes, 1.5 g/kg/day for 3 to 6 days; maximum dose 100 g/day if PEG is not available, one enema per rectum daily for 3 to 6 days:

Bisacodyl	2-10 years: 5 mg once a day >10 years: 5-10 mg once a day
Sodium docusate	<6 years: 60 ml >6 years: 120 ml
Sodium phosphate	1-18 years: 2.5ml/kg, maximum = 133 ml/ dose
Mineral oil	2-11 years: 30-60 ml once a day >11 years: 60-150 ml once a day

Note: PEG, polyethylene glycol. Sources: Tabbers et al, (2014); Taketomo et al, (2015)

Paediatric Trial

Medication Recommendations for constipation

Oral medications:

First line: PEG, with or without electrolytes, at a starting dose of 0.4 g/jg/day and adjusted to achieve desired effect. If PEG is not available, lactulose 1-2 g/kg, once a day, or 1.5-3 ml/kg/day

Second line or additional treatment -->

Milk of magnesia	2-5 years: 0.4 - 1.2 g/day, once or divided 6-11 years: 1.2 - 2.4 g/day, once or divided 12-18 years: 2.4 - 4.8 g/day, once or divided
Mineral oil	1-18 years: 1 - 3 ml/kg/day, once or divided, maximum 90 ml/day
Bisacodyl	3 - 10 years: 5mg/day > 10 years: 5 - 10 mg/day
Senna	2-6 years: 4.4 - 6.6 mg at bedtime, maximum dose 6.6 mg twice a day 6-12 years: 8.8 - 13.2 mg at bedtime, maximum dose 13.2 mg twice a day >13 years: 17.6 - 26.4 mg at bedtime, maximum dose 26.4 mg twice a day

Note: PEG, polyethylene glycol. Sources: Tabbers et al, (2014); Taketomo et al, (2015)

Drugs used in the management of chronic stypsis

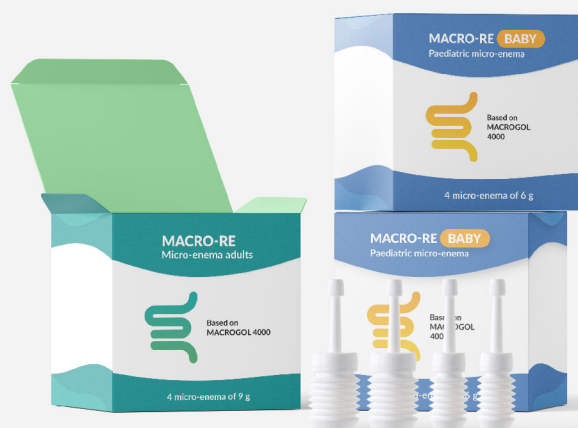
Several treatments, ranging from older over-the-counter (OTC) laxatives to newer prescription medications, are available for patients with chronic constipation. **Most patients (96%) seeking advice for constipation have already attempted self-medication with over-the-counter (OTC) drugs.**

- Bulk-forming laxatives
- Stimulant laxatives
- Faecal softeners
- Osmotic laxatives
- Bowel cleansing preparations
- Peripheral opioid-receptor antagonists
- 5HT4-receptor agoists

Johanson, J. F. and Kralstein, J. Chronic constipation: a survey of the patient perspective. *Aliment.Pharmacol.Ther.* 2007; 25: 599-608. Schiller, L. R. Review article: the therapy of constipation. *Aliment.Pharmacol.Ther* 2001; 15: 749-763.



Comparison between PEG and other osmotic laxatives



Osmotic laxatives include poorly absorbed sugars (Lactulose, Sorbitol), Glycerol, PEG and Magnesium salts. **The most studied osmotic laxatives are Macrogols and Lactulose** and there are well-designed RCTs that support their efficacy in the treatment of chronic constipation.

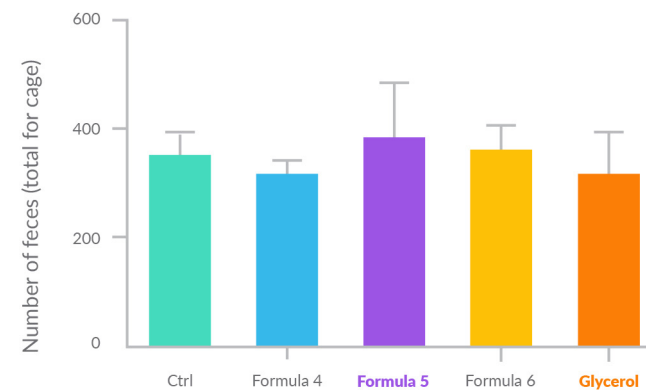
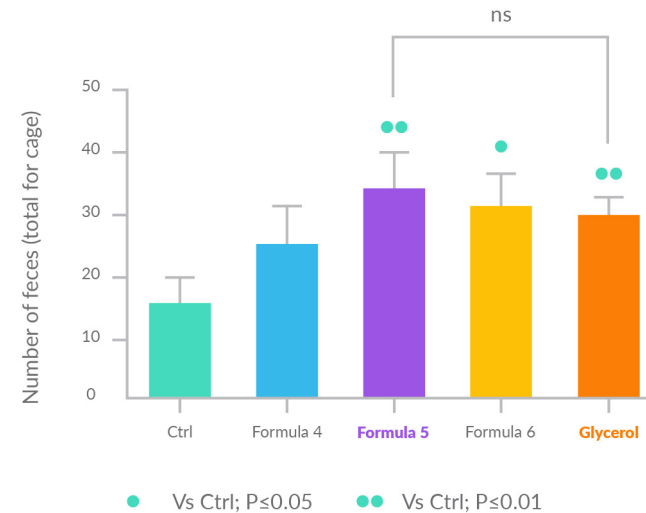
PEGs are superior to Lactulose in increasing stool frequency and reducing effort. Lactulose is degraded by the colon and can cause flatulence, swelling, abdominal cramps, nausea and diarrhea. **PEGs are less likely than lactulose to produce swelling and flatulence, as Macrogols are inert and are not degraded by colon bacteria.**

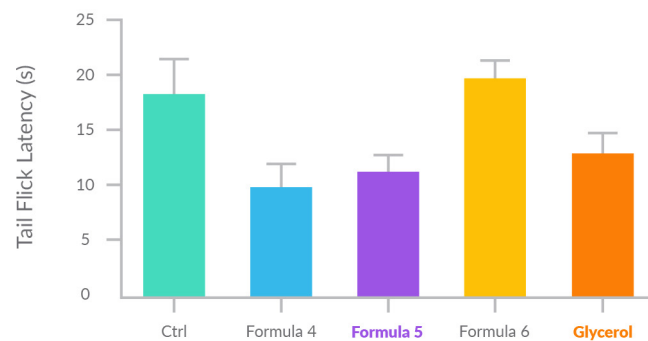
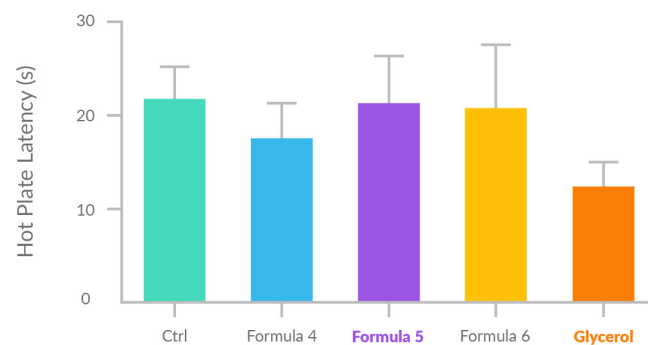
Louis Wing Cheong Liu Chronic constipation: Current treatment options Can J Gastroenterol. 2011 Oct; 25(Suppl B): 22B-28B. Wald, A. Chronic constipation: advances in management. Neurogastroenterol.Motil. 2007; 19: 4-10.

PEG vs Glycerol

Efficacy

On mice, the efficacy of our product (**formula 5**) on constipation is not inferior to glycerol (indeed, in statistical terms, it is slightly higher) both after 4 hours and after 24 hours.





PEG vs Glycerol

Rectal burning

In chronic (two weeks) Glycerol is pro-nociceptive (increases pain sensitivity) and irritating as evidenced by the data on the hot plate (central pain model) and tail flick (peripheral pain model).

No effect was observed for ISIPEG micro-enema (formula 5).



www.velitnb.com
info@velitnb.com