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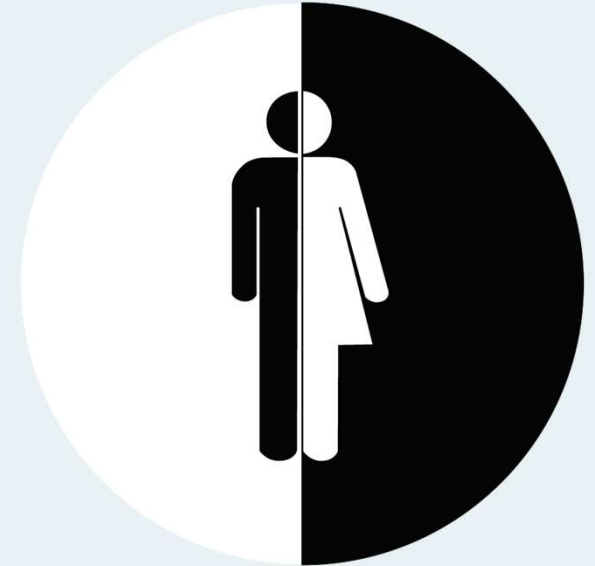
- Constipation – some background facts
- Laxatives – Advantages and Disadvantages
- PEG as laxative
- Clariant's offering in API Polyethylene glycols



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CONSTIPATION

- Some Background Facts



What is constipation?

A healthy frequency of a bowel movement are 3 bowel movements per day to 3 per week.

A constipation is chronic if two of the following symptoms appear for more than three months^[1] :

- Strong pressing
- Lumpy or hard stool
- Incomplete emptying
- Manual support for bowel movements
- Less than 3 bowel movements per week

Chronic constipation might have a big impact on people's lives with an influence in life quality^[2] and can be a cause for hemorrhoidal disease.



1. Longstreth, G.F., et al., *Functional bowel disorders*. Gastroenterology, 2006. **130**(5): p. 1480-91

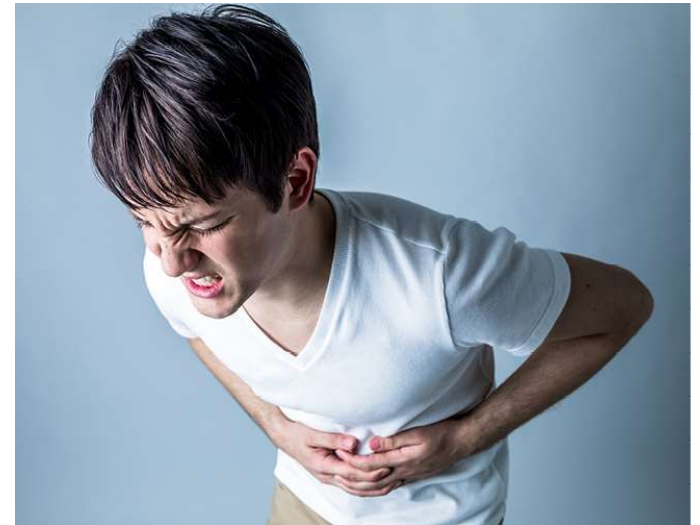
2. Sun, S.X., et al., Impact of chronic constipation on health-related quality of life, work productivity, and healthcare resource use: an analysis of the National Health and Wellness Survey. *Dig Dis Sci*, 2011. **56**(9): p. 2688-95

Talking about... constipation

5 – 15 % of the German population suffers from chronic constipation. The frequency increases with age and women are more affected than men [3,4].

Common reasons for constipation:

- stress, travelling (different food or time change)
- low fiber diet
- suppression of the bowel movement
- long colon transit
- hormone conversion during pregnancy or menopause
- Side-effect of certain diseases (e.g. multiple sclerosis, irritable colon, Parkinson's disease) and medicaments



3. Suares, N.C. and A.C. Ford, *Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis*. Am J Gastroenterol, 2011. **106**(9): p. 1582-91.

4. Wald, A., et al., *A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation*. Aliment Pharmacol Ther, 2008. **28**(7): p. 917-30.

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LAXATIVES

- Advantages and disadvantages



Common Laxatives types against constipation and how they work

| NATURAL LAXATIVES | | STIMULANT LAXATIVES | OSMOTIC LAXATIVES |
|---|---|--|--|
| Fibres e.g. Psyllium fibres | Leaves & blossoms e.g. Senna plants | e.g. Bisacodyl & Sodium Pico sulphate | e.g. Lactulose & PEG |
| <ul style="list-style-type: none"> – containing Polysaccharide^[5], build a gel with water in the colon – By this the stool is enlarged and softens | <ul style="list-style-type: none"> – containing Anthraquinone, which stimulate the mobility of the colon – – Stimulate the secretion which leads to a softer stool | <ul style="list-style-type: none"> – Directly attracting the nerves in the colon and stimulate the mobility of the colon (peristalsis) by this – Inhibit water resorption in the colon and stimulate secretion which leads to softer stool | <ul style="list-style-type: none"> – Attract water, enhance the stool volume and soften the stool |

5. www.mucofalk.de/html (01.06.2021)

Common Laxative types: Advantages & Disadvantages

| | NATURAL LAXATIVES | | STIMULANT LAXATIVES | OSMOTIC LAXATIVES | |
|---------------|--|--|---|---|--|
| | Fibres e.g. Psyllium fibres | Leaves & blossoms e.g. Senna plants | e.g. Sodium Pico sulphate | Lactulose | PEG ^[7] |
| Advantages | <ul style="list-style-type: none"> ✓ Suitable for long term therapy | <ul style="list-style-type: none"> ✓ More effective than Lactulose^[6] | <ul style="list-style-type: none"> ✓ Possible to be taken while breastfeeding ✓ Easy dosage ✓ Possible use starting from 4 years old | <ul style="list-style-type: none"> ✓ Recommended during pregnancy. | <ul style="list-style-type: none"> ✓ Low resorption from the body ✓ Recommended during pregnancy^[6] ✓ More effective and less side effects than Lactulose^[9] ✓ Possible use starting from 2 years old**^[8] ✓ Low gastrointestinal side effects ✓ Suitable for long-term therapy ✓ Aroma free types suitable for diabetic^[8] |
| Disadvantages | <ul style="list-style-type: none"> – Not recommended to use in combination with other medicine as adsorption could be delayed or prevented by the gel^[5] – Not recommended below the age of 12 years – side effects include gas and bloating | <ul style="list-style-type: none"> – Not recommended below the age of 12 years – Cramping is often observed – Not recommended for long term use in combination with other medicine such as diuretics, cortisone, cardiac glycosides – No data for long time use available – Can cause allergic reaction | <ul style="list-style-type: none"> – Cramping is often observed – Sudden urgency might occur – Fast reaction time might lead to unpredictable situations. – Habituation effect is noticed in some cases – No data for use during pregnancy – Not suitable for long-term therapy | <ul style="list-style-type: none"> – Might contain fructose, which might cause allergies. – Partially resorbed by the body – Could lead to gas in the colon. – Less effective for long colon transit times^[6] – Not recommended below the age of 14 years | |

6. Andresen V et al; AWMF S2k-Leitlinie Chronische Obstipation: Definition, Pathophysiologie, Diagnostik und Therapie, 2013, p. 23-26

7. DiPalma JA et al. South Med J. 2007;100:1085-1090 8. www.movicol.de/patientenratgeber Inside Health 2018 p.6-8

9. Pare P, Fedorak RN. Can J Gastroenterol Hepatol. 2014;28:549-557

** special products for Children available with prescription

Common Laxative types: Side effects are much lower with PEGs

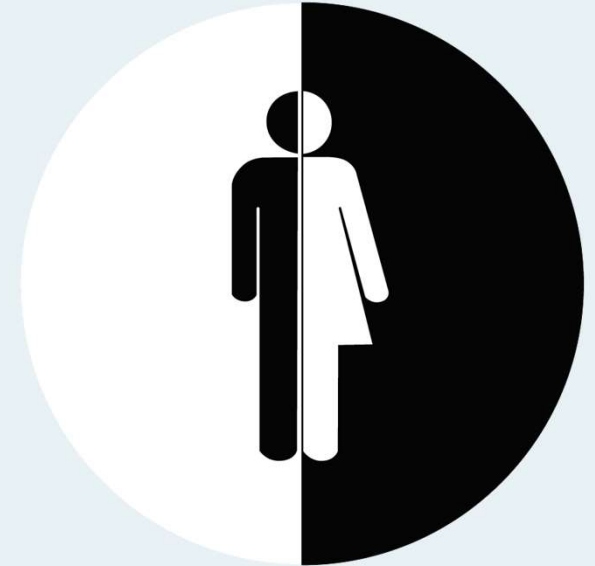
| SIDE EFFECTS* | PSYLLIUM FIBRES^[5] (NATURAL LAXATIVES) | SENNA PLANTS^[10] (NATURAL LAXATIVES) | STIMULANT LAXATIVES (E.G. SODIUM PICOSULPHATE^[11]) | LACTULOSE^[12] (OSMOTIC LAXATIVE) | PEG^[7,13] (OSMOTIC LAXATIVE) |
|--|--|--|--|--|--|
| Bloating | Incidental | | | Oftentimes | |
| Cramping | | Possible | Oftentimes | Oftentimes | |
| Stomach indisposition | | | Oftentimes | Oftentimes | |
| Nausea | | | Incidental | | |
| Diarrhoea | | Possible | Very often | Very often | |
| Dizziness | | | Incidental | | |
| Habituation effect | | | Possible | | |
| Absorption & Metabolism | | | Yes | Yes | |

[* Categories of side effects](#)

10. [Abführtee mit Sennesblättern bei gelegentlicher Verstopfung - Sidroga](#) 11. [dulcolax-np-tropfen-beipackzettel.pdf / \(30.06.2021\)](#)
12. [2016-12_50064085_GI_160x520.indd \(hexal.biz\) / \(06.06.2021\)](#) 13. [Patient Resources | MiraLAX® HCP / \(30.06.2021\)](#)

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PEG AS LAXATIVES



What is PEG?

- PEG is the abbreviation for a synthetic polymer group called Polyethylene glycol.
- Made by anionic polymerization of Ethylene oxide, it results into a polymer with the common formula $H-(OCH_2-CH_2)_n-OH$
- Known also under its pharmaceutical name Macrogol and it is used already since decades as pharmaceutical ingredient in the Pharmaceutical industry.
- Overall, they are described in various regional and the large international pharmacopoeias such as:
 - European Pharmacopoeia (Ph. Eur.)
 - Japanese Pharmacopoeia (J. P.)
 - US Pharmacopoeia (USP-NF)
- The products with a mean molecular weight of 3350 g/mol and 4000 g/mol are known as Active Pharmaceutical Ingredients (“API”) to give relief from constipation.
- There is also a US monograph for laxative formulation with PEG 3350 available.

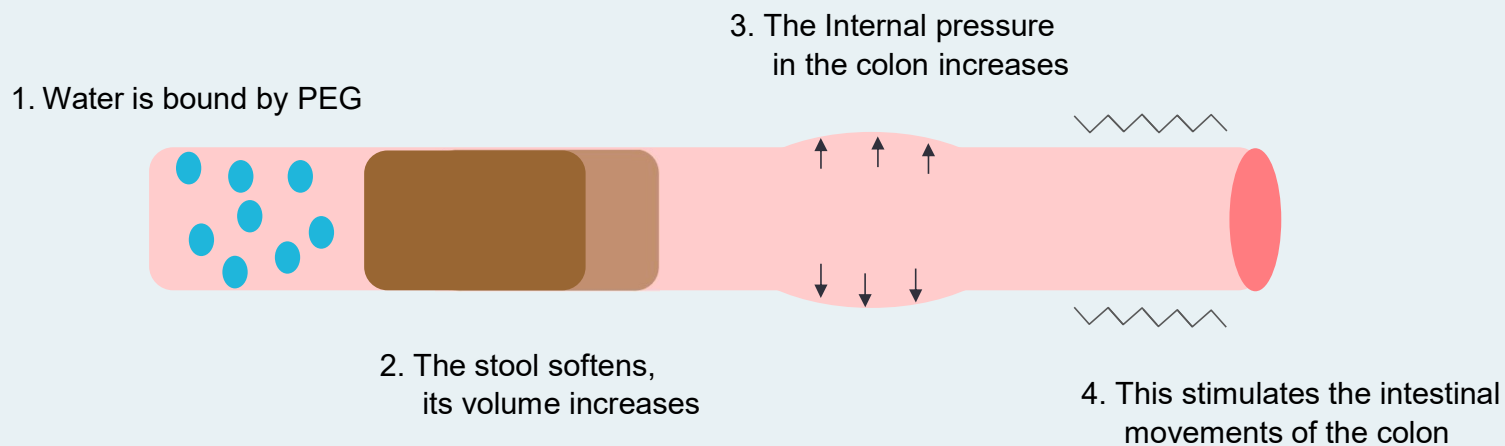
PEG as laxative

- PEG in laxative formulations is an osmotic agent, which is very gentle to the body.
- PEG is a very hygroscopic substance and shows therefore better effectiveness than other osmotic agents.
- Due to its polymeric nature, it is showing a very low resorption to the body.
- It is excreted completely and not absorbed by the digestive tract.
- Therefore, there is no influence by this API to the patient's diet.
- Furthermore, this results into low gastrointestinal side effects.
- Formulations with PEG as API suitable for long-term therapy and recommended during pregnancy.
- In combination with salts in the formulation the electrolytic balance of the body is not affected by these laxatives.
- Special PEG formulations could be used already by children > 2 years also for long term use.^[13]
- High efficacy and low side-effects of PEG makes it the golden standard for colonoscopy and pre-surgical treatment worldwide.

PEG as API – how does it work?

PEG has an osmotic effect, that means it binds water and makes the stool become softer and easier to drain.

This process takes place in overall 4 steps: ^[14]



Typical PEG-based formulation types against constipation*

| PEG | SOLID POWDER FORMULATIONS** | | | | LIQUID FORMULATIONS** | |
|------|---|---|---|--|---|--|
| | without electrolytes | | with electrolytes | | without electrolytes | with electrolytes |
| | pure | + other ingredients | | | | |
| 3350 | Formulation containing 100% PEG, no other ingredients, main dosage of PEG: 17 g | | Formulation containing ,> 85% PEG, electrolytes, sweetener / flavour main dosage of PEG: 2,95 / 5,9 g | Formulation containing 95% PEG, electrolytes, sweetener / flavour main dosage of PEG: 13,125 g | | Formulation containing appr. 50% PEG, electrolytes, purified water, sweetener / flavour, preservatives |
| 4000 | Formulation containing 100% PEG, no other ingredients, main dosage of PEG: 10 g | Formulation containing >99% PEG, with sweetener / flavour, main dosage of PEG: 10 g | Formulation containing ,> 85% PEG, electrolytes, sweetener / flavour main dosage of PEG: 7.3 g | | Formulation containing appr. 50 % PEG, purified water, sweetener / flavour, preservatives | |

* concentrating on the adult formulations and disregarding the different flavour types.

**composition and type of PEG depends also on the country & region

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CLARIANT'S OFFERING in API Polyethylene glycols



Clariant Polyethylene Glycols – Pharma Quality with long experience

- More than 30 years experience in producing Polyethylene glycols for the Pharmaceutical Industry
- Marketing Polyethylene glycols under the name “Polyglykol” and “VitiPure”
- Offering the whole range of possible molecular weights (200 to 35000 g/mol)
- Available excipient and API ranges.
- Offered in various physical forms (liquid, pastes, flakes (S), sprayed powders (PS), milled powders (P/PF))
- Specified according to General requirements of the 3 international pharmacopoeias (Ph. Eur., USP-NF, JP)



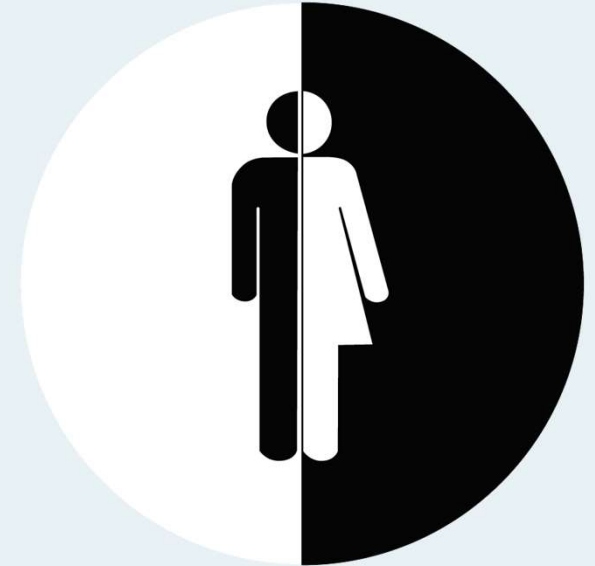
Clariant API Polyethylene Glycols – a tool-box for the individual laxative formulation

- More than 25 years experience in producing API Polyethylene glycols.
- Available in various physical forms available suitable for your final formulation (flake, sprayed powders, milled powders)
- Specified according to General requirements of the 3 international pharmacopoeias (Ph. Eur., USP-NF, JP)
- Registered at various authorities to support your dossier (e.g. CEP, DMF, China)
- PEG dedicated reactors to avoid cross contamination.
- Audited by the authorities for GMP compliance.



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BACKUP



Categories of side effects

| CATEGORY | |
|--------------------|---|
| very often | More than 1 of 10 patients |
| often | 1 to 10 of 100 patients |
| incidental | 1 to 10 of 1.000 patients |
| rarely | 1 to 10 of 10.000 patients |
| very rarely | Less than 1 of 10.000 patients |
| not common | Frequency cannot be estimated based on available data |