Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

RAZALAX ADULT
RAZALAX CHILDREN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Razalax adult
Each single-dose container contains:
Active ingredient: Glycerol 6.75 g

Razalax children
Each single-dose container contains:
Active ingredient: Glycerol 2.25 g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal solution (Enema).
Yellow to brown, dense liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Constipation

4.2 Posology and method of administration

Posology

Adults: 1 or 2 single-dose adult containers in 24 hours.
Even in the event of severe constipation, do not introduce more than 2 doses into the rectum at any one time.

Children: 1 or 2 single-dose child containers in 24 hours.
Even in the event of severe constipation, do not introduce more than 2 doses into the rectum at any one time.

4.3 Contraindications

RAZALAX ADULT and RAZALAX CHILDREN are contraindicated in the following cases:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- acute abdominal pain or of unknown origin;
- nausea or vomiting;
- intestinal obstruction or stenosis;
- rectal bleeding of unknown origin;
- acute haemorrhoids with pain and bleeding;
- severe state of dehydration.

4.4 Special warnings and precautions for use

Continuous use of laxatives can be habit-forming and can cause other problems.

Laxatives should be avoided in patients experiencing:
• Persistent unexplained change in bowel habits
• Palpable mass in the abdomen or the pelvis
• Persistent rectal bleeding without anal symptoms
• Narrowing of stool caliber
• Unexplained weight loss, iron deficiency anaemia, fever, or nocturnal symptoms

Family history of colon cancer, or inflammatory bowel disease.

Laxatives must be used as infrequently as possible, and never for more than seven days.
Use for longer periods of time requires a medical prescription after adequate examination of the individual case. The treatment of chronic or recurrent constipation always requires medical attention for a diagnosis, the prescription of drugs and supervision during the therapy. It is also advisable that the elderly and individuals who are in poor health consult a doctor before taking the medicine. Misuse of laxatives can cause persistent diarrhoea with consequent loss of water, mineral salts (especially potassium) and other essential nutrients. In more severe cases of misuse, dehydration or hypopotassaemia may occur, which can lead to heart or neuromuscular dysfunctions, especially in the case of simultaneous treatment with cardiac glycosides, diuretics or corticosteroids.
Misuse of laxatives, especially contact laxatives (stimulating laxatives), can cause drug tolerance (and, therefore, the possible need to progressively increase the dosage), chronic constipation and loss of normal intestinal functions (intestinal atony).
During episodes of constipation, it is first advisable to correct dietary habits by supplementing a daily diet with sufficient fibre and water.
When using laxatives it is advisable to drink at least 6-8 glasses of water or other liquids per day, so as to promote the softening of the stool.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other drugs have been observed.

4.6 Fertility, pregnancy and lactation

There have not been adequate, well-controlled studies on the use of this medicinal product in pregnancy or during breastfeeding.
Even if there are no clear contraindications to using this medicine in pregnancy and during breastfeeding, it is only recommended to take this medicine if needed and under medical supervision.

4.7 Effects on the ability to drive and use machines

Razalax has no influence on the ability to drive and use machines.
However, it is possible for undesirable effects to occur during treatment and so it is useful to know the response to the medicinal product before driving or using machines.

4.8 Undesirable effects

The only effects that may be seen are irritation to the rectal area. These are usually mild and do not require medical intervention.

Undesirable effects observed during treatment in clinical trials and supplemented with those collected during the post-marketing experience are listed in the table below, reported

according to the System Organ Class (using MedDRA terminology) and according to the following frequency:
Very common ≥1/10;
Common ≥1/100, <1/10;
Uncommon ≥1/1,000, <1/100;
Rare ≥1/10,000, <1/1,000;
Very rare <1/10,000;
Not known (the frequency cannot be estimated from the available data).

The available data are insufficient to establish the frequency of the individual effects listed:

Gastrointestinal disorders	
Not known	Abdominal cramps*, abdominal colic, diarrhoea**, anal irritation.

* usually isolated
** with loss of fluids and electrolytes

Isolated cramps or abdominal colic and diarrhoea are more frequent in cases of severe constipation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://reportsideffect.health.gov.il/drugs/home.

4.9 Overdose

No cases of overdose have been reported. In any case, excessive doses (misuse of laxatives, frequent or prolonged use or with excessive doses) may cause abdominal pain and persistent diarrhoea with consequent loss of water, mineral salts (especially potassium) and other essential nutrients. The fluid and electrolyte losses must be replenished.
Electrolyte imbalances are characterised by the following symptoms: thirst, vomiting, weakness, oedema, bone pain (osteomalacia) and hypoalbuminaemia.
In more severe cases, dehydration or hypopotassaemia may occur, which can lead to heart or neuromuscular dysfunctions, especially in the case of simultaneous treatment with cardiac glycosides, diuretics or corticosteroids.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: laxatives.

ATC code: A06AG04

Glycerine aids evacuation by locally stimulating the rectal mucous, through contact, without involving the distal portions of the intestine.
The muscle contraction causes the expulsion of faeces within a short space of time and, at the same time, eliminates all residue of the stimulant liquid.
Thanks to its hygroscopic and osmotic properties, glycerine also recalls water to the intestinal lumen, which softens the faeces and stimulates rectal muscle contraction. Glycerine also lubricates the stool.
The micro-enema also includes wheat starch, which has an emollient, protective action on mucous; the extract of malva and camomile help improve local tolerability.

5.2 Pharmacokinetic properties

Glycerine-based preparations for rectal use act as laxatives without the drug being absorbed by the intestinal mucous. When present in the intestinal lumen, glycerine is in fact able to perform its therapeutic action not as a consequence of its systemic absorption, but simply on the basis of a physical mechanism.
Orally-administered glycerine is readily absorbed by the intestine and metabolised with carbon monoxide and glycogen or used in the synthesis of fats.

5.3 Preclinical safety data

The literature has no reports of toxic effects following the use of glycerine.
The scientific literature reports different acute oral toxicity values in rats (LD50 from >5,000 to 58,400 mg/kg) and mice (LD50 from 4,250 to 38,000 mg/kg). The acute oral LD50 value ranges from 7,750 to 10,000 mg/kg of body weight, and from 18,000 to 27,000 mg/kg of body weight in guinea pigs and rabbits, respectively.
A dermal LD50 value of 18,700 mg/kg/day has been reported in rabbits. LD50 values for glycerol were between 4,420 and 10,100 mg/kg of body weight, and between 8,600 and 9,500 mg/kg of body weight in rats and mice, respectively, following intraperitoneal administration. The LD50 values after intravenous administration ranged between 4,250 and 6,700 mg/kg of body weight in rats, 4,250 and 4,370 mg/kg of body weight in mice, and 53,000 mg/kg of body weight in rabbits. Glycerol is much more toxic after subcutaneous administration (LD50 = 91 - 100 mg/kg of body weight) in mice and in rats, on the basis of the haemolytic effect. Nevertheless, no reliability has been assigned to these acute toxicity data for IP, IV or SC administration. No acute toxicity data through inhalation is reported for glycerol.
After 3 days of repeated oral exposure to glycerol, through gastric probe in rats, a LOAEL of 950 mg/kg of body weight is recorded, on the basis of local irritation of the gastro-intestinal tract. In three-day repeated dose toxicity studies in dogs, a NOEL of 950 mg/kg of body weight is recorded, on the basis of local effects on the GI tract. In a 2-year dietary study, a NOEL of 10.00 mg/kg/day was established. Repeated cutaneous application of glycerol for 45 weeks in rabbits, with a posology of 8 hours/day, 5 days/week, resulted in a NOEL of 5,040 mg/kg/day, which was the highest dose tested.
A LOAEL of 678 mg/kg of body weight was recorded in a 14-day inhalation toxicity study in rats (5 days/week, 6 hours/day, for a total of 10 exposures), on the basis of the local effects on the epithelium of the upper respiratory tract. In the 13-week inhalation study (with respiratory volume of 6 l/h for 5 days/week) in rats, a NOAEL of 165 mg/kg of body weight was recorded.

<u>Genetic toxicology</u>
Most of the studies on genotoxicity reported negative genotoxicity results for glycerol. Glycerol did not cause any mutation in the Ames tests that used four strains of Salmonella typhimurium with and without metabolic activation (rats and hamsters S-9) at concentrations up to 10,000 µg/plate. Glycerol did not cause any statistically significant increase in chromosomal aberrations at concentrations up to 1,000 ug/ml in gene mutation tests on mammal cells.
The in vivo study on rats (dominant lethal assay) at the dose of 10, 100 and 1,000 mg/kg of body weight produced a mutagenic effect on cells, which translated to post-implantation deaths. In another in vivo study conducted on rats at a dose level of 1,000 mg/kg of body weight, glycerol was reported to be non-mutagenic.

<u>Carcinogenicity</u>
There is insufficient data to assess the carcinogenicity of glycerol. There are no studies conducted according to modern regulatory guidelines. Data from studies not based on guidelines investigating the promotion of tumours in male mice suggest that the oral administration of glycerol up to 20 weeks had a weak effect on promoting the formation of lung tumours. In the same studies, treatment with glycerol alone (administered in drinking

water) did not lead to an increase in the number of mice with tumours compared to the control groups. Overall, these data do not raise concerns for potential carcinogenicity.
The administration of glycerol for two years at a dose level up to 10,000 mg/kg of body weight/day did not cause an increase in the formation of tumours. The genotoxicity data on glycerol also reached the conclusion of a potential non-genotoxicity, which supports the non-carcinogenicity. Overall, glycerol does not raise concerns for potential carcinogenicity.

Teratogenicity
In rats, toxicity studies on development carried out at dosage levels of 13.1, 60.8, 282 and 1,310 mg/kg of body weight (dosage during GD 6-15) showed a NOEL of 1,310 mg/kg of body weight/day. Toxicity studies on development carried out in mice (dosage during GD 6-18) via oral administration, at dosage levels of 12.8, 59.4, 276 and 1,280 mg/kg of body weight resulted in a NOEL of 1,280 mg/kg of body weight/day. No maternal or foetal toxicity was observed in rabbits, via oral administration, at dose levels of 11.8, 54.8, 254.5 and 1,180 mg/kg of body weight (dosage during GD 6-18). The previous study reported a NOEL of 1180 mg/kg/day.
Therefore, glycerol has no teratogenic potential.

Fertility
A study performed on two generations of male and female rats at a dose level of 2,000 mg/kg of body weight/day did not indicate any effect on the reproductive function of the parents, any effect on growth, fertility or reproduction of the untreated generation F1, nor was there any histological change in the tissues of generation F1 and F2. The above study reported a NOEL of 2,000 mg/kg of body weight/day. The scientific literature mentions various studies on the effect of glycerol on fertility via intratesticular administration at different dose levels and different durations. Nevertheless, the relevance of intratesticular exposure is low and the reliability of such data is poor. Therefore, these data are not mentioned at this time.
The preclinical data are of little clinical relevance in the light of the vast experience gained from use of this drug in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water, Liquid mallow extract, Chamomile fluid extract, Wheat starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25^0C.

6.5 Nature and contents of container

RAZALAX ADULT - Bellows-shaped, white coloured bottles with cannula and cap on the top of the cannula in low density polyethylene (PE-EVA) (LDPE), available in box containing 6 single-dose containers, each of 9 g.

RAZALAX CHILDREN - Bellows-shaped, white coloured bottles with cannula and cap on the top of the cannula in low density polyethylene (PE-EVA) (LDPE), available in box containing 6 single-dose containers, each of 3 g.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER & IMPORTER

RAZ PHARMACEUTICS LTD.,
31 GESHER HAETZ ST., INDUSTRIAL PARK, EMEK HEFER, 3877701, ISRAEL

8. MARKETING AUTHORISATION NUMBERS

RAZALAX ADULT: 158-37-34394-00
RAZALAX CHILDREN: 158-38-34408-00

Revised in November 2026**.**

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