The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in May 2017

Procto-Glyvenol® Suppositories
Procto-Glyvenol® Cream

Composition
Active ingredients: tribenoside, lidocaine hydrochloride/ lidocaine.

Excipients
Suppositories: Hard fat #2 (Witepsol W35), Hard fat #1 (Witepsol E85)
Cream: Purified water, Paraffin, liquid, Stearic acid, Sorbitol liquid (non crystallizing), Cetyl Alcohol, Macrogol cetostearyl ether (Cetomacrogol-1000), Isopropyl Palmitate, Sorbitan stearate (Arlacel-60), Methyl parahydroxybenzoate, Propyl parahydroxybenzoate.

Pharmaceutical forms and quantity of active ingredient per unit
1 suppository (2 g) contains 400 mg of tribenoside and 40 mg of lidocaine. Yellowish-white and torpedo-shaped suppositories.
1 g of cream contains 50 mg of tribenoside and 21.2 mg of lidocaine hydrochloride. White and homogenous cream.

Indications/Possible uses
Suppositories: Local relief of haemorrhoids.
Cream: External & internal haemorrhoids.

Posology/Method of administration
Adults: During the acute phase of the disorder, apply the cream or suppository in the morning and evening; subsequently, reduce to one application of cream or one suppository a day.
30g of cream (1 tube) are enough for approximately 20-30 applications.
Avoid contact with the eyes.
Intended for adult use only; not suitable for children.

Contraindications
Hypersensitivity to the active ingredients or excipients, according to the composition.

Warnings and precautions
Where there is bleeding in the anal area or where faecal blood is suspected as well as in the onset of other unusual symptoms, a medical examination with a view to diagnosis is advised.
If symptoms appear for the first time, self-medication should not last longer than 7 days.
Repeated treatments should only take place following diagnosis confirmed by a doctor.
Procto-Glyvenol should be used with caution in patients with severely impaired liver function.
There is no clinical experience in children.
Avoid contact with the eye, not for oral use.
Procto-Glyvenol cream contains cetyl alcohol, which may lead to local skin reactions (e.g. contact dermatitis). The cream also contains methyl and propyl parahydroxybenzoate; these substances may trigger allergic reactions (possibly delayed).

Interactions
No interaction studies have been performed.

Pregnancy/Breastfeeding
There is not enough data concerning the use in pregnant women.
No animal experiments exist on tribenoside or tribenoside in combination with lidocaine. Also, it is not known whether tribenoside crosses the placental barrier. Lidocaine shows some toxic effect on the embryo. Given these conditions, Procto-Glyvenol should not be used during pregnancy, particularly during the first three months, except when absolutely necessary.
Lidocaine can enter maternal milk; the advantages for the mother will have to be weighed against the risks for the child. As a precaution a choice has to be made between ending treatment and ending breastfeeding.

Effect on ability to drive and to operate machinery
No relevant studies have been performed.

Adverse events
Undesirable effects are listed below, classified by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system
Very rare: anaphylactic reaction
Heart
Very rare: Cardiovascular disorders
Skin
Rare: urticaria
Very rare: angioedema
Respiratory organs
Very rare: bronchospasm
Reactions at site of application
Rare: pruritus, rash, pain.
Very rare: Facial oedema

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).
Additionally, you may also report to GSK Israel (il.safety@gsk.com)

Overdose
No cases of overdosing have been reported.
In the event of accidental oral ingestion, gastric lavage is recommended, together with symptomatic treatment as well as general supportive measures.

Properties/Effects
ATC Code: C05AD01, C05AX05
The effect of tribenoside is based on the one hand on reducing capillary permeability and increasing vascular tone, and on the other hand on its local properties as an anti-inflammatory and antagonist to a whole series of endogenous substances that play a role as mediators in the occurrence of inflammation and pain.
Lidocaine is a local anaesthetic agent and relieves the pain, burning and itching caused by haemorrhoids.

Pharmacokinetics
Absorption
Systemic bioavailability of tribenoside in suppository form is only 30% compared to oral administration (capsules). Approximately 2-20% of tribenoside is absorbed through the skin from Procto-Glyvenol cream. 2 hours after rectal administration of a suppository (400 mg of tribenoside), maximum plasma concentrations of 1µg/ml of tribenoside and its metabolites are found. Lidocaine is readily absorbed from mucous membranes, but only moderately from intact skin. After rectal administration, the bioavailability of lidocaine is approx. 50%. Peak plasma concentrations of 0.70 µg/ml are reached 122 minutes after administration of a suppository of 300 mg lidocaine.
Distribution
The binding of lidocaine to plasma proteins, particularly alpha 1-acid glycoprotein, is variable and dependant on the concentration (approximately 60-80% at concentrations of 1-4 µg/ml).
Metabolism
In the body, tribenoside is highly metabolised. Lidocaine is rapidly metabolised in the liver.
Elimination

Tribenoside: After insertion of a suppository 20-27% of the dose is excreted in the urine in the form of metabolites.
Lidocaine: Less than 10% is excreted unchanged; the metabolites are excreted in the urine.

Preclinical data
No relevant preclinical data is available regarding tribenoside or the combination of tribenoside and lidocaine.
Mutagenicity studies on lidocaine have given negative results. On the other hand there are indications suggesting a mutagenic effect of a lidocaine metabolite, 2, 6–xylidine, produced in rats and possibly also in humans. These indications come from in vitro tests using this metabolite at very high, almost toxic, concentrations. Currently there are no indications that the mother substance, lidocaine, itself is also mutagenic. Moreover, 2, 6 -xylidine showed tumorigenic potential in a study on carcinogenicity carried out in rats involving transplacental exposure and post-natal treatment of the animals for 2 years. In this highly sensitive test system, malignant and benign tumours were observed at very high doses, specifically in the nasal cavity (ethmoturbinals). Given that the relevance of these effects to humans may not be excluded with sufficient certainty, high doses of lidocaine should never be given for longer periods of time.
Studies on toxicity in reproduction carried out on lidocaine gave no indications suggestive of a teratogenic property but embryotoxicity has been observed (reduction of foetal weight).
Behavioural changes have been observed in rats bred from female rats who, during pregnancy, received a dose of lidocaine almost equivalent to the maximum dose recommended for humans.

Specific comments
Stability
The medication must not be used after the date following the wording “EXP” on the packaging.

Comments regarding storage
Store Procto-Glyvenol Suppositories and Procto-Glyvenol cream out of the reach of children.
Store Procto-Glyvenol Suppositories and Procto-Glyvenol below 25ºC.

Manufacturer
Novartis Consumer Health SA, Switzerland
Route De I’Etraz 1260 Nyon, Switzerland

Packs
Suppositories: 10 suppositories. Sealed polyethylene and polypropylene aluminium foil.
Cream: 30 g. Aluminium tube with a protective inner coating, a cap and a nozzle.

Registraton Holder
GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

Registration numbers
Cream: 044-65-23919-00
Suppositories: 067-40-23920-00

ProGly DR v1