SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Soolantra

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cream contains 10 mg of ivermectin.

Excipient(s) with known effect:
One gram of cream contains 35 mg of cetyl alcohol, 25 mg of stearyl alcohol, 2 mg of methyl parahydroxybenzoate (E218), 1 mg of propyl parahydroxybenzoate (E216) and 20 mg of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.
White to pale yellow hydrophilic cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Soolantra is indicated in the topical treatment of inflammatory (papulopustular) lesions caused by rosacea in adults.

4.2 Posology and method of administration

Posology

One application a day for up to 4 months. Soolantra should be applied daily over the treatment course. The treatment course may be repeated.
In case of no improvement after 3 months, the treatment should be discontinued.

Special population

Renal impairment

No dosage adjustment is necessary.

Hepatic impairment
Caution should be exercised in patients with severe hepatic impairment.

Elderly patients
No dosage adjustment is necessary in the geriatric population (see also section 4.8).

Paediatric population
Soolantra is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Soolantra in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Cutaneous use only.
Cutaneous application of a pea-size amount of medicinal product to each of the five areas of the face: forehead, chin, nose, and each cheek. The medicinal product should be spread as a thin layer across the entire face, avoiding the eyes, lips and mucosa.

Soolantra should be applied only to the face.
Hands should be washed after applying the medicinal product.
Cosmetics may be applied after the medicinal product has dried.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients may experience transient aggravation of rosacea, which usually resolves within 1 week under continuation of the treatment as might be expected due to a reaction to the dying Demodex mites.
In case of severe worsening with a strong dermal reaction, the treatment should be discontinued.

Soolantra has not been studied in patients with renal or hepatic impairment.

The medicinal product contains:
- cetyl alcohol and stearyl alcohol which may cause local skin reactions (e.g. contact dermatitis),
- methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed),
- and propylene glycol which may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed (see section 5.2 for Biotransformation).

Concomitant use of Soolantra with other topical or systemic medicinal products for the treatment of rosacea has not been investigated.

In vitro studies have shown that ivermectin is primarily metabolised by CYP3A4. Consequently, caution is advised when ivermectin is administered concomitantly with potent CYP3A4 inhibitors as the plasma exposure may be significantly increased.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the topical use of ivermectin in pregnant women. Oral reproductive toxicity studies have shown that ivermectin is teratogenic in rats and rabbits (see section 5.3), however due to the low systemic exposure following topical administration of the product at the proposed posology, there is a low safety concern for a human foetus. Soolantra is not recommended during pregnancy.

Breast-feeding
Following oral administration, ivermectin is excreted in human milk in low concentrations. Excretion in human milk following topical administration has not been evaluated. Available pharmacokinetic/ toxicological data in animals have also shown excretion of ivermectin in milk. A risk to a suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Soolantra therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of ivermectin on fertility are available. In rats, there was no effect on mating or fertility with ivermectin treatment.

4.7 Effects on ability to drive and use machines

Soolantra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are skin burning sensation, skin irritation, pruritus and dry skin, all occurring in 1% or less of patients treated with the medicinal product in clinical trials.
They are typically mild to moderate in severity, and usually decrease when treatment is continued.
No meaningful differences in the safety profile were observed between subjects 18 to 65 years and subjects >65 years of age.

Tabulated list of adverse reactions
The adverse reactions are classified by System Organ Class and frequency, using the

following convention: 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) and were reported with Soolantra in clinical studies (see Table 1).

Table 1 - Adverse reactions

System Organ Class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	Common	Skin burning sensation
	Uncommon	Skin irritation, pruritus, dry skin
	Not known	Erythema, dermatitis contact (allergic or irritant)
		Swelling face
	Not known	Rosacea aggravation*

* Adverse reaction reported from post-marketing data

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.

https://sideeffects.health.gov.il

4.9 Overdose

There are no reports of overdosage with Soolantra.

In accidental or significant exposure to unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, oedema, headache, dizziness, asthenia, nausea, vomiting, and diarrhoea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In case of accidental ingestion, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, other

dermatologicals, ATC code: D11AX22

Mechanism of action

Ivermectin is a member of the avermectin class. Avermectin has anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines. Anti-inflammatory properties of cutaneous ivermectin have been observed in animal models of skin inflammation. Ivermectin also causes death of parasites, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. The mechanism of action of Soolantra in treating the inflammatory lesions of rosacea is not known but may be linked to anti-inflammatory effects of ivermectin as well as causing the death of Demodex mites that have been reported to be a factor in inflammation of the skin.

Clinical efficacy and safety

Soolantra applied once daily at bedtime was evaluated in the treatment of inflammatory lesions of rosacea in two randomised, double-blind, vehicle-controlled clinical studies, which were identical in design. The studies were conducted in 1371 subjects aged 18 years and older who were treated once daily for 12 weeks with either Soolantra or vehicle.

Overall, 96% of subjects were Caucasian and 67% were female. Using the 5-point Investigator Global Assessment (IGA) scale, 79% of subjects were scored as moderate (IGA=3) and 21% scored as severe (IGA= 4) at baseline.

The co-primary efficacy endpoints in both clinical studies were the success rate based on the IGA outcome (percentage of subjects “clear” and “almost clear” at Week 12 of the study) and absolute change from baseline in inflammatory lesion counts. The IGA scale is based on the following definitions:

Table 2: Investigator Global Assessment (IGA) scale

Grad	**Grad**	**Clinical Description**
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

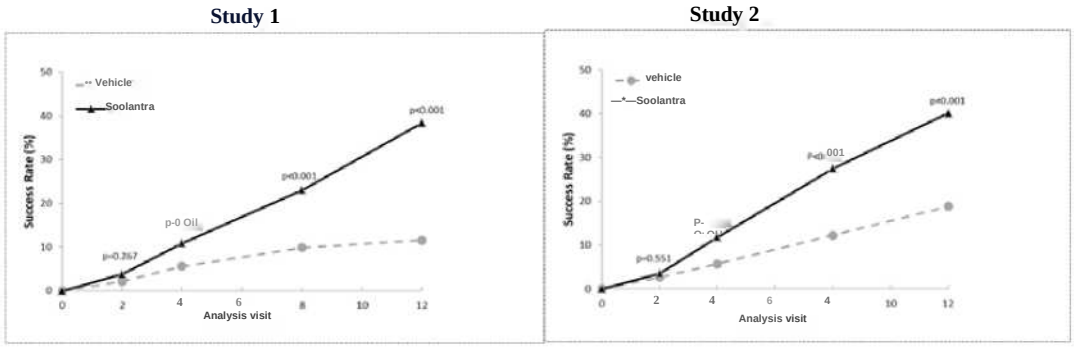
The results from both clinical studies demonstrated that Soolantra applied once daily for 12 weeks was statistically superior to vehicle cream in terms of IGA success rate and absolute change in inflammatory lesion counts ($p<0.001$, see table 3 and Figure 1, Figure 2, Figure 3 and Figure 4).

The following table and figures present efficacy outcomes from both studies.

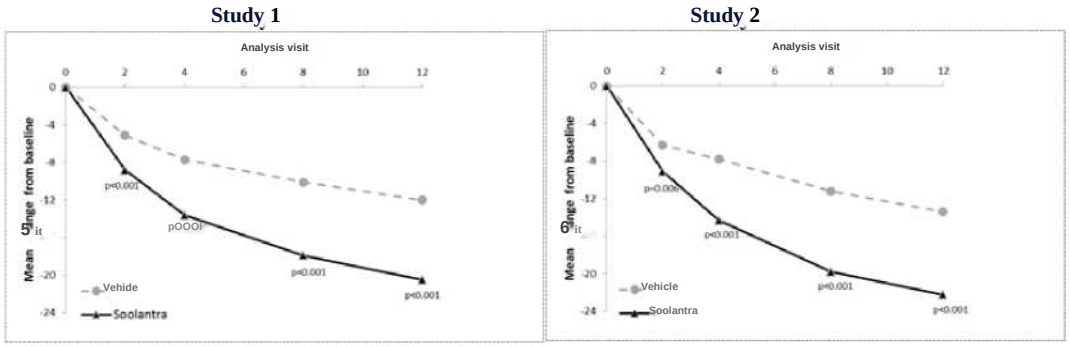
Table 3: Efficacy Results

	Study 1		**Study 2**	
	Soolantra (N=451)	**Vehicle (N=232)**	**Soolantra (N=459)**	**Vehicle (N=229)**
Investigator Global Assessment				
Number (%) of Subjects Clear or Almost Clear in the IGA at Week 12	173 (38.4)	27 (11.6)	184 (40.1)	43 (18.8)
Inflammatory Lesions				
Mean Inflammatory Lesion Count at Baseline	31.0	30.5	33.3	32.2
Mean Inflammatory Lesion Count at Week 12	10.6	18.5	11.0	18.8
Mean Absolute Change (%Change) in Inflammatory Lesion Count from Baseline at Week 12	-20.5 (-64.9)	-12.0 (-41.6)	-22.2 (-65.7)	-13.4 (-43.4)

Figures 1 and 2: IGA Success Rates Over Time in weeks



Figures 3 and 4: Mean Absolute Change in Inflammatory Lesion Counts from Baseline Over Time in weeks

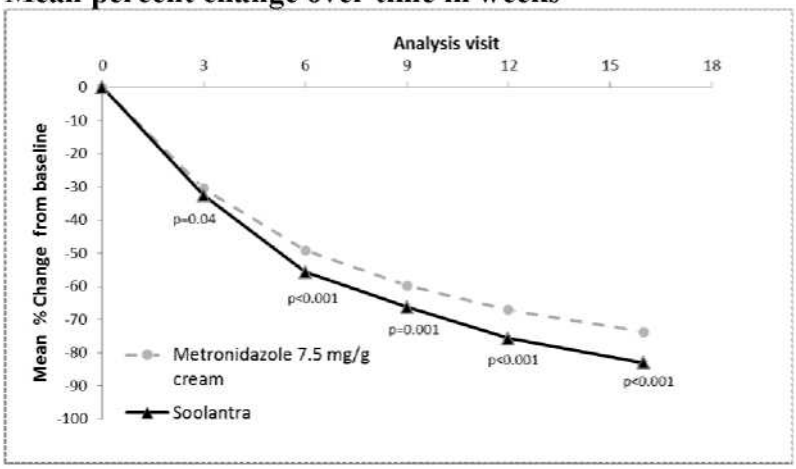


Soolantra was statistically superior to vehicle cream on the co-primary efficacy endpoints with a time to onset of efficacy of 4 weeks of treatment ($p<0.05$).

IGA was assessed during the 40-week extension of the two clinical studies and the percentages of subjects treated with Soolantra achieving an IGA score of 0 or 1 continued to increase up to Week 52. The Success Rate (IGA=0 or 1) at Week 52 was 71% and 76% in Studies 1 and 2, respectively.

The efficacy and safety of the medicinal product in the treatment of inflammatory lesions of rosacea were also evaluated in a randomised, investigator-blinded, active-controlled clinical study. The study was conducted in 962 subjects aged 18 years and older who were treated for 16 weeks with either Soolantra once daily or Metronidazole 7.5 mg/g cream twice daily. In this study, 99.7% of subjects were Caucasian and 65.2% were female; on the IGA scale, 83.3% of subjects were scored as moderate (IGA=3) and 16.7% scored as severe (IGA=4) at baseline (see figure 5).
The results of the study demonstrated that Soolantra was statistically superior to Metronidazole 7.5 mg/g cream on the primary efficacy endpoint (Mean Percent Change in Inflammatory Lesion Counts) with a reduction of 83.0% and 73.7% from baseline after 16 weeks of treatment for the ivermectin and metronidazole groups respectively ($p<0.001$). The superiority of Soolantra at Week 16 was confirmed on Success Rate based on IGA and Absolute Change in Inflammatory Lesion Counts (secondary endpoints ($p<0.001$).

Figure 5:
Mean percent change over time in weeks



Approximately 300 subjects aged 65 years and older were treated over all clinical trials with the medicinal product. No meaningful differences in the efficacy and safety profile were observed between elderly subjects and subjects 18 to 65 years of age.

The safety profile, as described in section 4.8 remained stable over conditions of long-term use as observed in long-term treatments up to one year.

5.2 Pharmacokinetic properties

Absorption

The absorption of ivermectin from Soolantra was evaluated in a clinical trial in adult subjects with severe papulopustular rosacea under maximal use conditions. At steady state (after 2 weeks of treatment), the highest mean (± standard deviation) plasma concentrations of ivermectin peaked within 10 ±8 hours post-dose (C_{max}: 2.1 ± 1.0 ng/mL range: 0.7 - 4.0 ng/mL) and the highest mean (± standard deviation) AUC_{0-24hr} was 36± 16 ng.hr/mL (range: 14-75ng.hr/mL). Ivermectin systemic exposure levels reached a plateau by two weeks of treatment (steady state conditions). In the longer treatment durations of the Phase 3 studies, ivermectin systemic exposure levels were similar to those observed after two weeks of treatment. At steady state conditions, the ivermectin systemic exposure levels (AUC_{0-24hr}:36 ±16 ng.hr/mL) were lower than those obtained following a single 6-mg oral dose of ivermectin in healthy volunteers (AUC_{0-24hr}:134 ± 66 ng.hr/mL).

Distribution

An in vitro study demonstrated that ivermectin is greater than 99% bound to plasma proteins and is bound primarily to human serum albumin. No significant binding of ivermectin to erythrocytes was observed.

Biotransformation

In vitro studies using human hepatic microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4.

In vitro studies show that ivermectin does not inhibit the CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 4A11 or 2E1. Ivermectin does not induce CYP450 enzyme expression (1A2, 2B6, 2C9 or 3A4) in cultured human hepatocytes.

Two major metabolites of ivermectin were identified in a maximal use clinical pharmacokinetic study and assessed during Phase 2 clinical studies (3"-O-demethyl ivermectin and 4a-hydroxy ivermectin). Similar to the parent compound, metabolites reached steady state conditions by 2 weeks of treatment, with no evidence of accumulation up to 12 weeks. Furthermore, the metabolites systemic exposures (estimated with C_{max} and AUC) obtained at steady state were much lower than those observed following oral administration of ivermectin.

Elimination

The terminal half-life averaged 6 days (mean: 145 hours, range 92-238 hours) in patients receiving a once daily cutaneous application of the medicinal product for 28 days, in the maximal use clinical pharmacokinetic study. Elimination is absorption-dependent following topical treatment with Soolantra.
Pharmacokinetics of ivermectin have not been studied in patients with renal and hepatic impairment.

5.3 Preclinical safety data

Repeat-dose studies up to 9 months via dermal application of ivermectin 10 mg/g cream in minipigs have not shown toxic effects or local toxicity at systemic exposure levels comparable to clinical exposure.

Ivermectin is not genotoxic in a battery of in vitro and in vivo tests. A 2-year carcinogenicity study via dermal application of ivermectin 10 mg/g cream in mice did not show any increased tumour incidence.

Reproductive toxicity studies after oral administration of ivermectin showed teratogenic effects in rats (cleft palates) and rabbits (carpal flexures) at high doses (exposure margin to the NOAEL at least 70-fold compared to the clinical exposure).

The neonatal toxicity in oral rat studies was not related to in utero exposure but to postnatal exposure through maternal milk which resulted in high levels of ivermectin in the brain and in plasma of offspring.
Ivermectin 10 mg/g cream has evidence of being skin irritant, sensitizing and photosensitising in Guinea pigs, but is not phototoxic.

Environmental Risk Assessment (ERA)

Ivermectin is very toxic for invertebrates and a risk has been identified for the aquatic, sediment and the terrestrial compartment. Care should be taken in order to prevent environmental contamination, in particular in the aquatic media.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Isopropyl palmitate
Cetyl alcohol
Macrogol cetostearyl ether
Stearyl alcohol
Sorbitan stearate
Propylene glycol
Oleyl alcohol
Phenoxyethanol
Dimeticone 20C Cst
Carbomer copolymer type B
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Disodium edetate
Citric acid monohydrate
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening: use within 6 months.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Tube:

2g, 15g, 30g, 45g, 60g plastic tubes having a high density polyethylene body structure with a high density polyethylene head, closed with a polyprpoylene screw cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Mitigation measures should be taken in order to prevent or reduce contamination, in particular the aquatic media.

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

7 Manufacturer: Laboratories Galderma, Alby sur Cheran, France

8. Registration holder: Rafa Laboratories Ltd. ,P.O.Box 405, Jerusalem 9100301

Registration number: 167-59-36606-99