

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206255Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOOLANTRA safely and effectively. See full prescribing information for SOOLANTRA.

SOOLANTRA™ (ivermectin) cream, 1%, for topical use
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

SOOLANTRA cream is indicated for the treatment of inflammatory lesions of rosacea. (1)

DOSAGE AND ADMINISTRATION

- Apply to the affected areas once daily. (2)
- Not for oral, ophthalmic or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 1%, supplied in tubes of 30 g, 45 g and 60 g. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

In controlled clinical trials with SOOLANTRA the most common adverse reactions (incidence $\leq 1\%$) included skin burning sensation and skin irritation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SOOLANTRA cream is indicated for the treatment of inflammatory lesions of rosacea.

2 DOSAGE AND ADMINISTRATION

Apply to the affected areas of the face once daily. Use a pea-size amount for each area of the face (forehead, chin, nose, each cheek) that is affected. Spread as a thin layer, avoiding the eyes and lips.

SOOLANTRA cream is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Cream, 1%.

Each gram of SOOLANTRA cream contains 10 mg of ivermectin in a white to pale yellow cream base. SOOLANTRA cream is supplied in tubes of 30 g, 45 g and 60 g.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical trials, 2047 subjects with inflammatory lesions of rosacea received SOOLANTRA cream once daily. A total of 1555 subjects were treated once daily for more than 12 weeks, and 519 for approximately one year.

Adverse reactions, reported in $\leq 1\%$ of subjects treated with SOOLANTRA cream for at least 3 months in vehicle-controlled clinical trials, included skin burning sensation and skin irritation.

7 DRUG INTERACTIONS

In vitro studies have shown that SOOLANTRA cream, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SOOLANTRA cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Note: The animal multiples of human exposure calculations were based on AUC comparisons. The maximum topical human dose (MTHD) of SOOLANTRA cream is 1 g applied once daily.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1.5, 4, and 12 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 6–17) to pregnant female rats. Maternal death occurred at 12 mg/kg/day (1909X MTHD). Cleft palate occurred in the fetuses from the 12 mg/kg/day (1909X MTHD) group. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 4 mg/kg/day (708X MTHD). Oral doses of 0.5, 1.5, 2.5, 3.5 and 4.5 mg/kg/day ivermectin were administered during the period of organogenesis (gestational days 7–20) to pregnant female rabbits. Maternal death occurred at doses ≥ 2.5 mg/kg/day (72X MTHD). Carpal flexure occurred in the fetuses from the 4.5 mg/kg/day (354X MTHD) group. Fetal weight decrease was noted at 3.5 mg/kg/day (146X MTHD). No treatment related effects on embryofetal toxicity were noted at 2.5 mg/kg/day (72X MTHD) and no treatment related effects on teratogenicity were noted at 3.5 mg/kg/day (146X MTHD).

A pre- and postnatal development study was conducted in rats. Oral doses of 1, 2 and 4 mg/kg/day ivermectin were administered to pregnant female rats during gestational days 6–20 and lactation days 2–20. Neonatal death occurred at doses ≥ 2 mg/kg/day. Behavior development of newborn rats was adversely affected at all doses.

8.3 Nursing Mothers

Following oral administration, ivermectin is excreted in human milk in low concentrations. Excretion in human milk following topical administration has not been evaluated. In oral studies in rats, ivermectin was excreted in the milk of nursing mothers and neonatal toxicity was observed in the litters. The blood-brain barrier in neonatal rats may not be fully developed at birth. Because of the potential for serious adverse reactions from SOOLANTRA cream in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of SOOLANTRA cream in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1371 subjects in the two pivotal clinical studies of SOOLANTRA cream, 170 (12.4%) were 65 and over, while 37 (2.7%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

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, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. 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.

11 DESCRIPTION

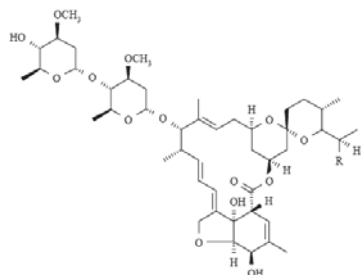
SOOLANTRA (ivermectin) cream, 1% is a white to pale yellow hydrophilic cream. Each gram of SOOLANTRA cream contains 10 mg of ivermectin. It is intended for topical use.

Ivermectin is a semi-synthetic derivative isolated from the fermentation of *Streptomyces avermitilis* that belongs to the avermectin family of macrocyclic lactones.

Ivermectin is a mixture containing not less than 95.0 % and not more than 102.0 % of 5-O-demethyl-22,23-dihydroavermectin A_{1a} plus 5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}, generally referred to as 22,23-dihydroavermectin B_{1a} and B_{1b} or H₂B_{1a} and H₂B_{1b}, respectively; and the ratio (calculated by area percentage) of component H₂B_{1a}/(H₂B_{1a} + H₂B_{1b}) is not less than 90.0 %.

The respective empirical formulas of H₂B_{1a} and H₂B_{1b} are C₄₈H₇₄O₁₄ and C₄₇H₇₂O₁₄ with molecular weights of 875.10 and 861.07 respectively.

The structural formulas are:



Component H₂B_{1a}: R = C₂H₅, Component H₂B_{1b}: R = CH₃.

SOOLANTRA cream contains the following inactive ingredients: carbomer copolymer type B, cetyl alcohol, citric acid monohydrate, dimethicone, edetate disodium, glycerin, isopropyl palmitate, methylparaben, oleyl alcohol, phenoxyethanol, polyoxyl 20 cetostearyl ether, propylene glycol, propylparaben, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of SOOLANTRA cream in treating rosacea lesions is unknown.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At therapeutic doses, SOOLANTRA cream is not expected to prolong QTc interval.

12.3 Pharmacokinetics

Absorption

The absorption of ivermectin from SOOLANTRA cream was evaluated in a clinical trial in 15 adult male and female subjects with severe papulopustular rosacea applying 1 g SOOLANTRA cream, 1% once daily. At steady state (after 2 weeks of treatment), the highest mean $\pm$ standard deviation) plasma concentrations of ivermectin peaked (T_{max}) at 10 ± 8 hours post-dose, the maximum concentration (C_{max}) was 2.10 ± 1.04 ng/mL (range: 0.69 - 4.02 ng/mL) and the area under the concentration curve (AUC_{0-24hr}) was 36.14 ± 15.56 ng.hr/mL (range: 13.69-75.16 ng hr/mL). In addition, systemic exposure assessment in longer treatment duration (Phase 3 studies) showed that there was no plasma accumulation of ivermectin over the 52-week treatment period.

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.

Metabolism

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 at therapeutic concentrations does not inhibit the CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 or 4A11, or induce 1A2, 2B6, 2C9 or 3A4.

Excretion

The apparent terminal half-life averaged 6.5 days (mean $\pm$ standard deviation: 155 ± 40 hours, range 92-238 hours) in patients receiving a once daily cutaneous application of SOOLANTRA cream for 28 days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year dermal mouse carcinogenicity study, ivermectin was administered to CD-1 mice at topical doses of 1, 3, and 10 mg/kg/day (0.1%, 0.3% and 1% ivermectin cream applied at 2 ml/kg/day). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 10 mg/kg/day (747X maximum topical human dose (MTHD)).

In a 2-year oral rat carcinogenicity study, ivermectin was administered to Wistar rats at gavage doses of 1, 3, and 9 mg/kg/day. A statistically significant increase in the incidence of hepatocellular adenoma was noted in males treated with 9 mg/kg/day (1766X MTHD) ivermectin. The clinical relevance of this finding is unknown. No drug-related tumors were noted in females up to the highest dose evaluated in this study of 9 mg/kg/day (1959X MTHD). No drug-related tumors were noted in males at doses ≤ 3 mg/kg/day (599X MTHD).

Ivermectin revealed no evidence of genotoxic potential based on the results of two in vitro genotoxicity tests (the Ames test and the L5178Y/TK^{+/+} mouse lymphoma assay) and one in vivo genotoxicity test (rat micronucleus assay).

In a fertility study, oral doses of 0.1, 1 and 9 mg/kg/day ivermectin were administered to male and female rats. Mortality occurred at 9 mg/kg/day (1027X MTHD). The precoital period was generally prolonged at 9 mg/kg/day. No treatment related effects on fertility or mating performance were noted at doses ≤ 1 mg/kg/day (68X MTHD).

14 CLINICAL STUDIES

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

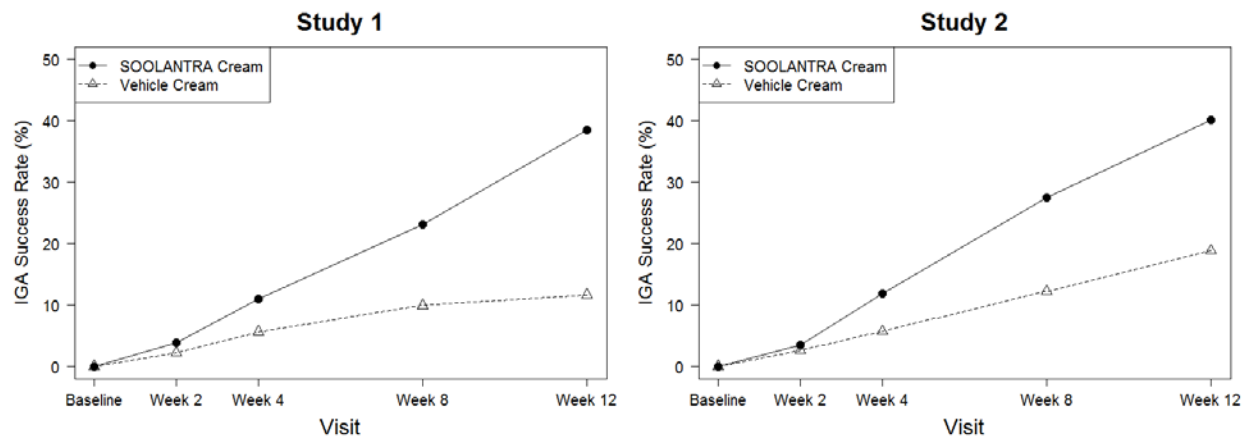
Overall, 96% of subjects were Caucasian and 67% were female. Using the 5-point Investigator Global Assessment (IGA) scale (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe), 79% of subjects were scored as moderate (IGA=3) and 21% scored as severe (IGA= 4) at baseline.

The co-primary efficacy endpoints in both pivotal trials were the success rate based on the IGA outcome (percentage of subjects "clear" and "almost clear") and absolute change from baseline in inflammatory lesion counts at Week 12. Table 1 presents the co-primary efficacy results at Week 12. SOOLANTRA cream was more effective than vehicle cream on the co-primary efficacy endpoints starting from 4 weeks of treatment in both studies, see Figures 1 through 4.

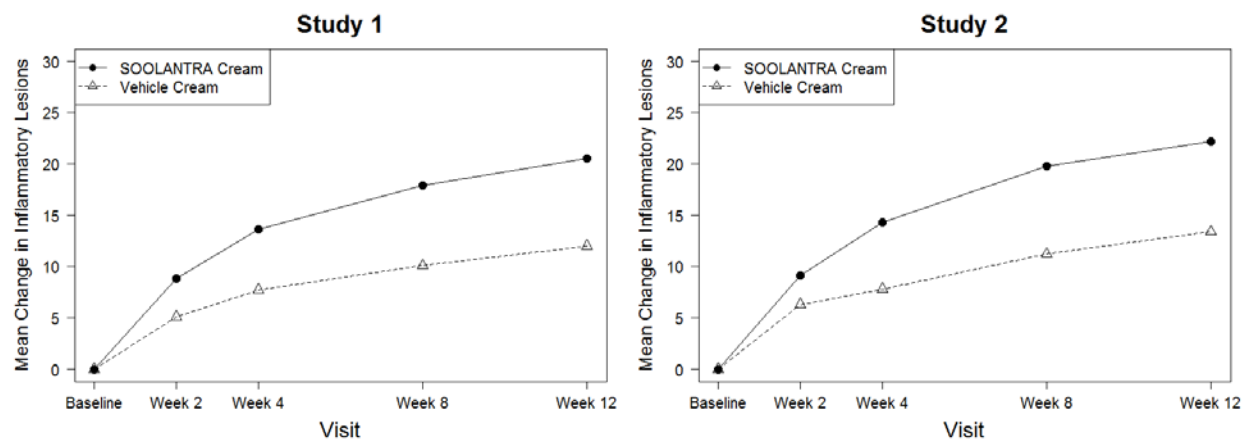
Table 1: Co-Primary Efficacy Results at Week 12

	Study 1		Study 2	
	SOOLANTRA Cream (N=451)	Vehicle Cream (N=232)	SOOLANTRA Cream (N=459)	Vehicle Cream (N=229)
Investigator Global Assessment:				
Number (%) of Subjects Clear or Almost Clear	173 (38.4%)	27 (11.6%)	184 (40.1%)	43 (18.8%)
Inflammatory Lesion Counts:				
Mean Absolute (%) Change from Baseline	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**



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



16 HOW SUPPLIED/STORAGE AND HANDLING

SOOLANTRA (ivermectin) cream, 1% is a white to pale yellow cream, supplied in a laminated tube with a child resistant cap in the following sizes:

30 gram **NDC 0299-3823-30**

45 gram **NDC 0299-3823-45**

60 gram **NDC 0299-3823-60**

Storage

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Patients using SOOLANTRA cream should receive the following instruction:

Keep out of reach of children.

Marketed by:

GALDERMA LABORATORIES, L.P.

Fort Worth, Texas 76177 USA

Manufactured by:

G Production Inc.

Baie d’Urfé, QC, H9X 3S4 Canada

Made in Canada.

PXXXXXX-0

Instructions for Use
SOOLANTRA (soo lan' trah)
(ivermectin) cream, 1 %

Important: SOOLANTRA™ cream is for use on the face only. Do not use SOOLANTRA cream in your eyes, mouth or vagina.

Read and follow the steps below so that you use SOOLANTRA cream correctly:

1. Open the tube of SOOLANTRA cream by gently pressing down on the child resistant cap and twist in the direction of the arrow (counterclockwise) as shown below. See Figures A and B. To avoid spilling, do not squeeze the tube while opening or closing.



Figure A



Figure B

2. To apply SOOLANTRA cream to your face, squeeze a pea-sized amount of SOOLANTRA cream from the tube onto your fingertip. See Figure C.



Figure C

3. Apply SOOLANTRA to the affected areas of your face once a day. Use a pea-sized amount of SOOLANTRA cream for each area of your face (forehead, chin, nose, each cheek) that is affected. Spread the cream smoothly and evenly in a thin layer. Avoid contact with your eyes and lips.
4. To close SOOLANTRA cream, gently press down on the child resistant cap and twist to the right (clockwise). See Figure D.



Figure D

How should I store SOOLANTRA cream?

- Store SOOLANTRA cream at room temperature between 68°F to 77°F (20°C to 25°C).

Keep SOOLANTRA cream out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Marketed by: GALDERMA LABORATORIES, L.P. Fort Worth, TX 76177 USA

Made in Canada.

Issued: December 2014

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Not for oral, ophthalmic, or intravaginal use.
To Open Tube: Push cap in and turn counterclockwise to remove cap.
Usual Dosage: Apply to the affected areas once daily. See package insert for complete prescribing information.
Each gram contains the active ingredient ivermectin 10 mg (1%) with the inactive ingredients carbomer copolymer type B, cetyl alcohol, citric acid monohydrate, dimethicone, edetate disodium, glycerin, isopropyl palmitate, methylparaben, oleyl alcohol, phenoxyethanol, polyoxyl 20 cetostearyl ether, propylene glycol, propylparaben, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol.
Storage: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F).
[See USP Controlled Room Temperature].
See carton closure for lot number and expiration.

NDC 0299-XXXX-XX

soolantra™
(ivermectin) cream, 1%

NET WT. 30 g

Rx only
For Topical Use Only
Keep Out of Reach of Children

GALDERMA

NDC 0299-XXXX-XX

soolantra™
(ivermectin) cream, 1%

NET WT. 30 g

Rx only
For Topical Use Only
Keep Out of Reach of Children

GALDERMA

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, TX 76177 USA
Made in Canada
P52477-0 Rev.: 09/14



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Exp.:
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JILL A LINDSTROM
12/19/2014