

8.5 Geriatric Use

One hundred and five subjects aged 65 and older were included in clinical trials with MIRVASO topical gel. No overall differences in safety or effectiveness were observed between subjects ≥ 65 years of age and younger adult subjects. Clinical studies of MIRVASO topical gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

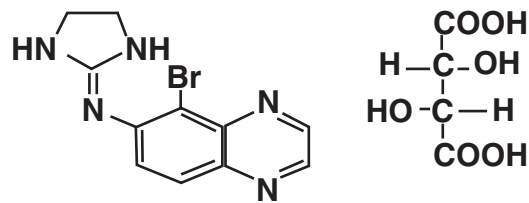
10 OVERDOSAGE

No information is available on overdose in adults with MIRVASO topical gel. Oral overdoses of other alpha-2 adrenergic agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

11 DESCRIPTION

MIRVASO (brimonidine) topical gel, 0.33% contains brimonidine tartrate, an alpha adrenergic agonist. The molecular formula of brimonidine tartrate is $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$. It has the following structural formula:



Chemically, brimonidine tartrate is 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. Brimonidine tartrate has a molecular weight of 442.24 and appears as white to slightly yellowish powder.

Each gram of MIRVASO (brimonidine) topical gel, 0.33% contains 5 mg of the active ingredient brimonidine tartrate (equivalent to 3.3 mg of brimonidine free base), in a white to light yellow opaque gel composed of the inactive ingredients carbomer homopolymer type B, glycerin, methylparaben, phenoxyethanol, propylene glycol, purified water, sodium hydroxide, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brimonidine is a relatively selective alpha-2 adrenergic agonist. Topical application of MIRVASO topical gel may reduce erythema through direct vasoconstriction.

12.3 Pharmacokinetics

Absorption

The absorption of brimonidine from MIRVASO topical gel was evaluated in a clinical trial in 24 adult subjects with facial erythema associated with rosacea. All enrolled subjects received once daily topical application of MIRVASO topical gel 1 gram to the entire face for 29 days.

Pharmacokinetic assessments were performed on Day 1, Day 15, and Day 29. The mean plasma maximum concentration (C_{max}) and area under the concentration-time curve (AUC) were highest on Day 15, with C_{max} and AUC values (\pm standard deviation) of 46 ± 62 pg/mL and 417 ± 264 pg.hr/mL, respectively. The systemic drug exposure was slightly lower on Day 29 indicating no further drug accumulation.

Metabolism

Brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 21-month oral (diet) mouse carcinogenicity study and a 24-month oral (diet) rat carcinogenicity study, no drug-related neoplasms were observed in mice at oral doses of brimonidine tartrate up to 2.5 mg/kg/day or in rats at oral doses of brimonidine tartrate up to 1 mg/kg/day.

In a dermal rat carcinogenicity study with MIRVASO topical gel, brimonidine tartrate was administered to Wistar rats at topical doses of 0.9 (0.03% gel), 1.8 (0.06% gel), and 5.4 mg/kg/day (0.18% gel) in males and 5.4 (0.18% gel), 30 (1% gel) during Days 1-343/10.8 (0.36% gel) thereafter, and 60 (2% gel) during Days 1-343/21.6 mg/kg/day (0.72% gel) thereafter in females once daily for 24 months. No drug-related neoplasms were observed in this study.

In a 12-month dermal photo-carcinogenicity study, topical doses of 0% (MIRVASO topical gel vehicle), 0.18%, 1% and 2% brimonidine tartrate gel were administered to hairless albino mice once daily, five days per week, with concurrent exposure to simulated sunlight. No drug-related adverse effects were observed in this study. The results of this study suggest that topical treatment with MIRVASO topical gel would not enhance photo-carcinogenesis.

Mutagenesis

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies, including the Ames test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in CD1 mice (a host-mediated assay, a cytogenetic study, and a dominant lethal assay).

Impairment of Fertility

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effects on male or female fertility at oral doses up to 1 mg/kg/day.

14 CLINICAL STUDIES

MIRVASO topical gel was evaluated for the treatment of moderate to severe, persistent (nontransient) facial erythema of rosacea in two randomized, double-blind, vehicle-controlled clinical trials, which were identical in design. The trials were conducted in 553 subjects aged 18 years and older who were treated once daily for 4 weeks with either MIRVASO topical gel or vehicle. Overall, 99% of subjects were Caucasian and 76% were female. Baseline disease severity was graded using a 5-point Clinical Erythema Assessment (CEA) scale and a 5-point Patient Self Assessment (PSA) scale, on which subjects scored either "moderate" or "severe" on both scales.

The primary efficacy endpoint in both pivotal trials was 2-grade Composite Success, defined as the proportion of subjects with a 2-grade improvement on both CEA and PSA measured at hours 3, 6, 9, and 12 on Day 29. Table 2 presents the efficacy results. In addition to Day 29, efficacy was evaluated on Day 15 and Day 1, and the results are presented in Figures 1 and 2 for Studies 1 and 2, respectively.

Table 2: Summary of 2-grade Composite Success on Day 29

Success	Study 1		Study 2	
	MIRVASO Topical Gel (N=129)	Vehicle Gel (N=131)	MIRVASO Topical Gel (N=148)	Vehicle Gel (N=145)
Hour 3	31%	11%	25%	9%
Hour 6	30%	10%	25%	9%
Hour 9	26%	10%	18%	11%
Hour 12	23%	9%	22%	10%

2-grade Composite Success: 2-grade improvement on CEA and 2-grade improvement on PSA.

Instructions for Use MIRVASO (Mer-VAY-soe) (brimonidine) topical gel Pump

Important: MIRVASO® topical gel is for use on the face only. Do not use MIRVASO topical gel in your eyes, mouth, or vagina.

Keep MIRVASO topical gel out of the reach of children.

If anyone, especially a child, accidentally swallows MIRVASO topical gel, they may have serious side effects and need to be treated in a hospital. Get medical help right away if you, a child, or anyone else swallows MIRVASO topical gel and has any of these symptoms:

- lack of energy, trouble breathing or stops breathing, a slow heart beat, confusion, sweating, restlessness, muscle spasms, or twitching.

Read and follow the steps below so that you use your MIRVASO topical gel correctly:

1. Push the cap down and turn it counter-clockwise until the cap can be removed. See Figures A and B. The clear sticker will break when opening for the first time.

Note: when the cap is removed, the pump is not child-resistant.

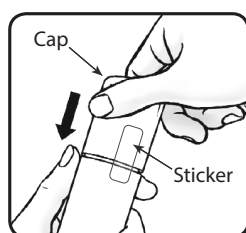


Figure A

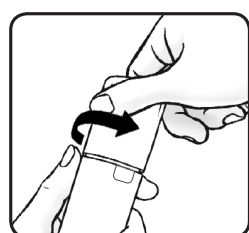


Figure B

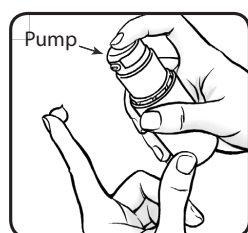


Figure C

Before the first use, prime the pump by pressing down several times until the medicine is dispensed onto your fingertip.

2. To apply MIRVASO topical gel to your face, dispense a pea-sized amount of MIRVASO topical gel from the pump onto your fingertip. See Figure C.
3. Apply a pea-sized amount of MIRVASO topical gel onto each of the five areas of your face (forehead, chin, nose, each cheek) 1 time each day. You will use a total of 5 pea-sized amounts of MIRVASO topical gel. Spread the gel

Figure 1: 2-grade Composite Success by Hour and Day for Study 1

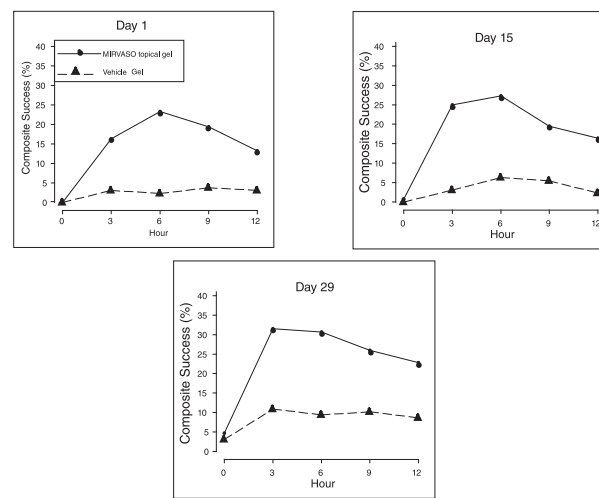
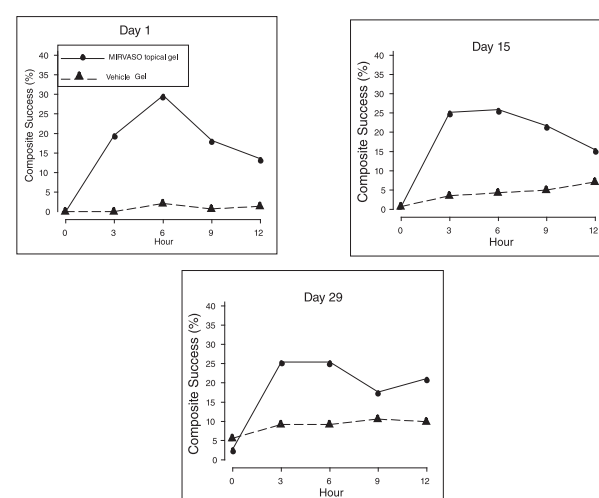


Figure 2: 2-grade Composite Success by Hour and Day for Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

MIRVASO (brimonidine) topical gel, 0.33% is a white to light yellow opaque gel, supplied in a laminated tube or pump with a child resistant cap in the following sizes:

30 gram tube NDC 0299-5980-30

30 gram pump NDC 0299-5980-35

45 gram tube NDC 0299-5980-45

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

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Patients using MIRVASO topical gel should receive the following information and instructions:

- This medication is to be used as directed by the physician.
- It is for external use only.
- MIRVASO topical gel should not be applied to irritated skin or open wounds.
- Avoid contact with the eyes and lips.
- Patients should wash their hands immediately after applying the medication.
- Some patients using MIRVASO topical gel may experience erythema, flushing or excessive whitening.
- Patients should report any adverse reactions to their physician.
- Keep out of reach of children

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smoothly and evenly in a thin layer over your face. Avoid contact with your eyes and lips. Do not apply MIRVASO topical gel to irritated skin or open wounds.

4. To close your MIRVASO topical gel pump, place the cap back on the pump. Push down and turn the cap to the right (clockwise) until it stops. The pump is child-resistant again. See Figure D.

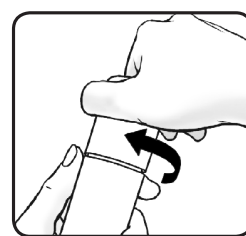


Figure D

5. Wash your hands right away after applying MIRVASO topical gel.

How should I store MIRVASO topical gel?

- Store MIRVASO topical gel at room temperature between 68°F to 77°F (20°C to 25°C).

Keep MIRVASO topical gel and all medicines out of the reach of children.

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

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