

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

MIRVASO Gel: brimonidine 3.3 mg/g

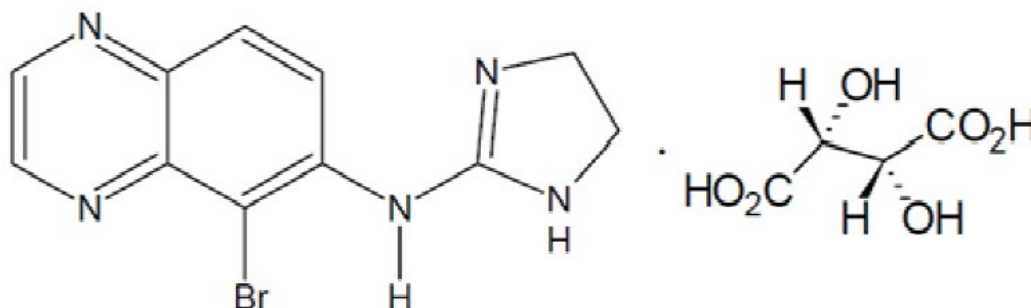
**Australian Approved Name (AAN):** brimonidine tartrate

**Chemical Names:** 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-(+)-tartrate; 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-(+)-tartrate

**Molecular Formula:** C<sub>11</sub>H<sub>10</sub>BrN<sub>5</sub>.C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>

**Molecular Weight:** 442.2 as the tartrate salt

**Structural Formula:** brimonidine tartrate



**CAS Number:** 70359-46-5

### DESCRIPTION

MIRVASO is a white to light-yellow opaque gel. One gram of MIRVASO gel contains brimonidine tartrate equivalent to brimonidine 3.3 mg.

### List of excipients

Carbomer 934P  
Methyl hydroxybenzoate (E218)  
Phenoxyethanol  
Glycerol  
Titanium dioxide  
Propylene glycol  
Sodium hydroxide  
Purified water

### PHARMACOLOGY

#### Mechanism of action and Pharmacodynamic effects

Brimonidine is a selective  $\alpha_2$ -adrenergic receptor agonist that is 1000-fold more selective for the  $\alpha_2$ -adrenergic receptor than the  $\alpha_1$ -adrenergic receptor.

Topical facial application of a highly selective  $\alpha_2$ -adrenergic receptor agonist is intended to reduce erythema through direct cutaneous vasoconstriction.

### **Pharmacokinetics**

The absorption of brimonidine from MIRVASO was evaluated in a relative bioavailability study in 23 adults with facial erythema of rosacea. All enrolled patients received 1 drop every 8 hours of a brimonidine 0.2% eye drops solution for 24 hours, followed by a once daily cutaneous application of the maximal quantity (1g) of MIRVASO for 29 days (intra-individual comparison of systemic exposure). After repeated cutaneous application of MIRVASO on facial skin, no drug accumulation in plasma was observed throughout the treatment duration: the highest mean ( $\pm$  standard deviation) plasma maximum concentration ( $C_{max}$ ) and area under the concentration-time curve from 0 to 24 hours ( $AUC_{0-24hr}$ ) were  $46 \pm 62$  pg/mL and  $417 \pm 264$  pg.hr/mL respectively. These levels are comparable to those obtained in patients treated with a 0.2% eye drops solution of brimonidine.

The pharmacokinetics and pharmacodynamics of MIRVASO have been primarily undertaken in Caucasian subjects and the effect of race or gender on the PK/PD is unknown.

The protein binding of brimonidine has not been studied. Brimonidine is extensively metabolised by the liver. Urinary excretion is the major route of elimination of brimonidine and its metabolites.

### **CLINICAL TRIALS**

The efficacy of MIRVASO in the treatment of moderate to severe facial erythema of rosacea has been demonstrated in two randomised, vehicle-controlled clinical trials, which were identical in design. The studies were conducted in 553 subjects aged 18 years and older who were treated once daily for 4 weeks with either MIRVASO or vehicle. Of these, 539 were included in the efficacy analysis at Day 29. 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.

The results from the pivotal clinical studies were consistent, demonstrating that MIRVASO was significantly more effective ( $p < 0.001$ ) in the reduction of facial erythema of rosacea than vehicle gel when applied once daily for 29 days. With respect to the primary endpoint of the pivotal studies (2-grade composite success defined as 2-grade improvement on both validated measures of the Clinician Erythema Assessment (CEA) and Patient Self-Assessment (PSA) at hours 3, 6, 9, and 12 on Day 29), once daily treatment with MIRVASO resulted in significantly greater success (17.6% to 31.5%;  $p < 0.001$ ) compared to vehicle treatment (8.6% to 10.9%). Therefore, MIRVASO was also demonstrated to be 3-4 times more effective than vehicle after 1 month of treatment (2- grade Composite Success at Day 29, see Table 1). In addition, treatment with MIRVASO had a rapid effect compared to vehicle gel (as per defined secondary endpoint of 1-Grade Composite Success for CEA and PSA at 30 minutes on Day 1,  $p < 0.001$ ), with sustained efficacy over at least 12 h (1-Grade Composite Success for CEA and PSA at hours 3, 6, 9, and 12 on Day 29, see Table 2).

**Table 1: Phase 3 pivotal studies results: 2-grade composite success on day 29**

Success	Study 1		Study 2	
	MIRVASO Gel (N=127) n/N (%)	Vehicle Gel (N=128) n/N (%)	MIRVASO Gel (N=142) n/N (%)	Vehicle Gel (N=142) n/N (%)
Hour 3	40/127 (31.5%)	14/128 (10.9%)	36/142 (25.4%)	13/142 (9.2%)
Hour 6	39/127 (30.7%)	12/128 (9.4%)	36/142 (25.4%)	13/142 (9.2%)
Hour 9	33/127 (26.0%)	13/128 (10.2%)	25/142 (17.6%)	15/142 (10.6%)
Hour 12	29/127 (22.8%)	11/128 (8.6%)	30/142 (21.1%)	14/142 (9.9%)
<b>Day 29 p-value</b>	<b>&lt;0.001</b>	-	<b>&lt;0.001</b>	-
<b>Day 29 odds ratio (95% CI)</b>	<b>3.75 (2.10, 6.70)</b>	-	-	<b>2.95 (1.69, 5.15)</b>

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

**Table 2: Phase 3 pivotal studies results: 1-grade composite success on day 29**

Success	Study 1		Study 2	
	MIRVASO Gel (N=127) n/N (%)	Vehicle Gel (N=128) n/N (%)	MIRVASO Gel (N=142) n/N (%)	Vehicle Gel (N=142) n/N (%)
Hour 3	90/127 (70.9%)	42/128 (32.8%)	101/142 (71.1%)	57/142 (40.1%)
Hour 6	88/127 (69.3%)	41/128 (32.0%)	92/142 (64.8%)	61/142 (43.0%)
Hour 9	81/127 (63.8%)	38/128 (29.7%)	95/142 (66.9%)	56/142 (39.4%)
Hour 12	72/127 (56.7%)	39/128 (30.5%)	76/142 (53.5%)	57/142 (40.1%)
<b>Day 29 p-value</b>	<b>&lt;0.001</b>	-	<b>&lt;0.001</b>	-

1-grade Composite Success: 1-grade improvement on CEA and 1-grade improvement on PSA.

These studies demonstrate that following a once daily application of MIRVASO, the typical daily pattern is rapid onset (in as little as 30 minutes) of noticeable reduction in erythema after the very first application, followed by a sustained peak therapeutic effect over several hours, with a visible therapeutic effect being maintained throughout the day.

No consistent relationship was observed between concentration of brimonidine gel formulations used or resulting systemic drug levels throughout the clinical development programme, and adverse reactions. Further, no tachyphylaxis or rebound effects (worsening of baseline erythema after cessation of treatment) were observed with use of MIRVASO for 29 days. In addition, subjects using MIRVASO concomitantly with other medications for the treatment of rosacea did not experience an increase of adverse reactions beyond that anticipated for each drug individually.

Concomitant use of MIRVASO with other medicinal products for the treatment of rosacea has not been systematically investigated. However, in the long term open-label study, the efficacy and safety of MIRVASO, as described above, was not affected by the concomitant use of cosmetics or other medicinal products (e.g. topical metronidazole, topical azelaic acid, and oral tetracyclines including low dose doxycycline) for the treatment of inflammatory lesions of rosacea in the relevant subpopulation (131/449 patients in the study who used concomitant rosacea medicinal product).

## **INDICATIONS**

MIRVASO is indicated for the treatment of facial erythema of rosacea in adult patients.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients; children under 18 years of age; therapy with concomitant monoamine oxidase inhibitor (MAOI), tricyclic or tetracyclic antidepressants, which affect noradrenergic transmission.

## **PRECAUTIONS**

A definite diagnosis of rosacea should be made before treatment with MIRVASO is considered

MIRVASO should not be applied on irritated skin or open wounds. If severe irritation or contact allergy occurs, treatment with MIRVASO should be discontinued.

Alpha adrenergic receptor agonists should be used with caution in patients:

- with severe or unstable or uncontrolled cardiovascular disease;
- with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thrombangiitis obliterans, scleroderma, or Sjögren's syndrome.

The medicinal product contains methylparahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed), and propylene glycol which may cause skin irritation.

### **Phototoxicity**

There were no studies investigating the safety and efficacy of MIRVASO in rosacea patients exposed to high levels of ultraviolet sun exposure. It is not known as to whether phototoxicity reactions may occur under these circumstances. Therefore, it is recommended that patients are advised to avoid excessive exposure to sunlight and UV light. Sunscreen may be applied after the application of MIRVASO (see Dosage and Administration).

### **Effects on fertility**

Brimonidine did not have a significant effect on fertility in rats at oral doses of up to 0.66 mg/kg/day.

### **Use in Pregnancy (Category B3)**

There are no adequate and well-controlled studies with the use of MIRVASO Gel in pregnant women. In rats, the drug crosses the placenta and enters the fetal circulation. Because animal reproduction studies are not always predictive of human response, MIRVASO Gel should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. In pregnant rats, brimonidine was associated with maternotoxicity and increased early resorptions/post-implantation losses and decreased pup viability and body weights at estimated exposures (based on AUC) of 180 times the expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits and caused abortions at exposures about 12 times greater than those expected in humans. In both rats and rabbits, brimonidine was not teratogenic.

### **Use in Lactation**

It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate and some of its metabolites have been shown to be excreted in milk of lactating rats. In the absence of human data, MIRVASO Gel should not be used during breast-feeding. Because of the potential for serious adverse reactions from MIRVASO

Gel 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.

### **Paediatric Use**

The safety and efficacy of MIRVASO in children aged less than 18 years have not been established.

### **Use in the Elderly**

The experience of use of Mirvaso in patients aged above 65 years is limited. Therefore, caution should be exercised in the elderly.

One hundred and four elderly patients (>65 years of age) were included in Phase 3 clinical trials with MIRVASO Gel. No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

### **Use in renal or hepatic impairment**

MIRVASO has not been studied in patients with renal or hepatic impairment, thus use caution with these patients.

### **Genotoxicity**

Brimonidine tartrate was not genotoxic in assays for chromosomal damage (Chinese hamster cells in vitro, in vivo bone marrow cytogenetic assay and a dominant lethal assay). In assays for gene mutations in *S. typhimurium* and *E. coli*, brimonidine gave a positive response in one *S. typhimurium* strain without metabolic activation; other strains gave negative results. Brimonidine is not considered to pose a genotoxic hazard to patients.

### **Carcinogenicity**

Brimonidine did not induce compound-related carcinogenic effects in either mice or rats in life span dietary studies.

Brimonidine gel was not carcinogenic in rats after dermal application for up to 2-years at up to 5.4 mg/kg/day and 21.6 mg/kg/day in male and female rats, respectively, corresponding to systemic exposures (based on plasma AUC) representing 516- and 2566-fold the maximal human exposure in males and females, respectively. Brimonidine gel was not photo(co)carcinogenic in hairless mice with concomitant UV irradiation.

### **Effect on Ability to Drive and Use Machinery**

No specific studies on the effects of MIRVASO on the ability to drive and use machinery have been performed, however, no cases of fatigue and/or drowsiness were reported with MIRVASO during clinical trials. In addition, given the pharmacology and pharmacokinetics demonstrated with MIRVASO gel, negligible or no impact on driving and using machinery is expected when MIRVASO is used as recommended.

## **INTERACTIONS WITH OTHER MEDICINES**

No interaction studies have been performed.

MIRVASO is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy (for example selegiline or moclobemide) and patients on tricyclic (such as imipramine) or tetracyclic (such as maprotiline, mianserin or mirtazapine) antidepressants which affect noradrenergic transmission (see **Contraindications**).

Brimonidine can also interact with tricyclic and tetracyclic antidepressants affecting the metabolism and uptake of circulating amines. It is not known whether the concurrent use of these agents with MIRVASO in humans can lead to resulting interference with the vasoconstrictive effect.

Although specific drug-drug interactions studies have not been conducted with MIRVASO, the possibility of an additive or potentiating effect with Central Nervous System depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

No data on the level of circulating catecholamines after MIRVASO administration are available. Thus, caution is advised in patients taking medications which can affect the metabolism and uptake of circulating amines (eg. chlorpromazine, methylphenidate, reserpine).

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with alpha adrenergic receptor agonists or interfere with their activity ie. agonists or antagonists of the adrenergic receptor (eg. isoprenaline, prazosin).

Brimonidine may cause clinically insignificant decreases in blood pressure in some patients. Caution is therefore advised when using medicinal products such as anti-hypertensives and/or cardiac glycosides concomitantly with brimonidine.

#### **ADVERSE EFFECTS**

Overall, MIRVASO gel was shown to be well tolerated, with the most commonly (ie.  $\geq 1\%$ ) reported adverse drug reactions being erythema, pruritus, flushing and skin burning sensation, all occurring in 1.2 to 3.3% of patients. Adverse reactions were usually transient, mild to moderate in severity, and usually did not require discontinuation of treatment.

#### **Erythema and Flushing**

Some subjects in the clinical trials discontinued use of MIRVASO topical gel because of erythema or flushing. The effect of MIRVASO topical gel may begin to diminish hours after application. For some subjects in the clinical trials, erythema was reported to return with a severity greater than at baseline.

Intermittent flushing occurred in some subjects treated with MIRVASO topical gel. The onset of flushing relative to the application of MIRVASO topical gel varied ranging from approximately 30 minutes to several hours.

Erythema and flushing appeared to resolve after discontinuation of MIRVASO topical gel.

#### **Adverse reactions**

Adverse reactions that occurred in at least 1% of subjects treated with MIRVASO topical gel once daily for 29 days and for which the rate for MIRVASO topical gel exceeded the rate for vehicle are presented in Table 3.

**Table 3: Adverse Reactions Reported in Clinical Trials by at Least 1% of Subjects Treated for 29 Days**

Preferred Term	MIRVASO Topical Gel (N=330) n (%)	Vehicle Gel (N=331) n (%)
<b>Subjects with at least one adverse reaction, Number (%) of Subjects</b>	<b>109 (33)</b>	<b>91 (28)</b>
Erythema	12 (4%)	3 (1%)
Flushing	9 (3%)	0
Skin burning sensation	5 (2%)	2 (1%)
Dermatitis contact	3 (1%)	1 (<1%)
Dermatitis	3 (1%)	1 (<1%)
Skin warm	3 (1%)	0
Paraesthesia	2 (1%)	1 (<1%)
Acne	2 (1%)	1 (<1%)
Pain of skin	2 (1%)	0
Vision blurred	2 (1%)	0
Nasal congestion	2 (1%)	0

#### Open-label, Long-term Study

An open-label study of MIRVASO topical gel when applied once daily for up to one year was conducted in subjects with persistent (nontransient) facial erythema of rosacea. Subjects were allowed to use other rosacea therapies. A total of 276 subjects applied MIRVASO topical gel for at least one year. The most common adverse events ( $\geq 4\%$  of subjects) for the entire study were flushing (10%), erythema (8%), rosacea (5%), nasopharyngitis (5%), skin burning sensation (4%), increased intraocular pressure (4%), and headache (4%).

#### Allergic contact dermatitis

Allergic contact dermatitis to MIRVASO topical gel was reported in approximately 1% of subjects across the clinical development program. Two subjects underwent patch testing with individual product ingredients. One subject was found to be sensitive to brimonidine tartrate, and one subject was sensitive to phenoxyethanol (a preservative).

### **DOSAGE AND ADMINISTRATION**

Once daily application.

MIRVASO should be applied in five small pea-size amounts, the total estimated to be no more than 1 g, are applied to the main areas of the face (ie. forehead, chin, nose, each cheek) once daily after the usual cleansing routine. No more than 1g of gel per day should be used, and application to the eyes, eyelids, lips, mouth and membrane of the inner nose should also be avoided.

For optimal facial treatment, it is recommended that application is smooth and even across all areas of the face to avoid accidental omission of areas, and minimise noticeable contrast between treated and untreated areas.

Other creams or lotions such as cosmetics and sunscreen may be applied after the application of MIRVASO.

## **OVERDOSAGE**

No information is available on overdose in adults with MIRVASO. However, serious adverse effects following inadvertent ingestion of MIRVASO by two young children of one clinical study subject have been reported. The children experienced symptoms consistent with previously reported oral overdoses of  $\alpha_2$ -agonist in young children. Both children were reported to have made a full recovery within 24 hours.

Oral overdoses of other  $\alpha_2$ -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. In the event of accidental application to the eyes, flush with a topical ocular irrigant.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

## **PRESENTATION AND STORAGE CONDITIONS**

One gram of MIRVASO gel contains 3.3mg of brimonidine equivalent to 5 mg of brimonidine tartrate. For a full list of excipients, see **Description**.

### **Nature and contents of the container**

Laminated plastic tubes with a plastic child-resistant closure for the 10g and 30g pack sizes.

Pack sizes: 2g (Physician's sample), 10g and 30g.

Not all pack sizes may be marketed.

### **Storage:**

Store below 25°C.

Do not refrigerate below 2°C

## **NAME AND ADDRESS OF SPONSOR**

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**Attachment 1: Product information for AusPAR Mirvaso Brimonidine tartrate Galderma Australia Pty Ltd PM-2013-01459-1-5 Date of Finalisation 23 January 2015 This Product Information was approved at the time this AusPAR was published.**

**POISON SCHEDULE OF THE MEDICINE**

S4 – PRESCRIPTION MEDICINE

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**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 4<sup>th</sup> August 2014**