New Zealand Datasheet

1 PRODUCT NAME
MIRVASO

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Brimonidine 3.3 mg/g gel

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
MIRVASO is indicated for the treatment of facial erythema of rosacea in adult patients.

4.2 Dosage and method of administration
Once daily application. Cutaneous use only.

Treatment should be initiated with a smaller amount of gel (less than the maximum) for at least one week. The amount of gel can then be increased gradually based on tolerability and patient response.

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 (forehead, chin, nose and both cheeks) to avoid accidental omission of areas, and minimise noticeable contrast between treated and untreated areas.

Mirvaso should be applied to the face only. Hands should be washed immediately after applying MIRVASO.

Other creams or lotions such as cosmetics and sunscreen may be applied after the application of MIRVASO. These products should not be applied immediately before the daily application of Mirvaso; they may be used only after the applied Mirvaso has dried.

4.3 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.

4.4 Special warnings and precautions for use
A definite diagnosis of rosacea should be made before treatment with MIRVASO is considered

MIRVASO should not be applied on irritated skin (including following laser therapy) or open wounds. If severe irritation or contact allergy occurs, treatment with MIRVASO should be discontinued.

The concomitant use of systemic alpha adrenergic receptor agonists may potentiate the undesirable effects of this class of medicinal products and 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.

This product is not for use in the paediatric population. Keep out of reach of children.

Exacerbation of rosacea symptoms was reported in patients treated with Mirvaso. Treatment should be initiated with a small amount of gel and the dose increased gradually, based on tolerability and response to treatment.

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

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 begins to diminish hours after application. In some patients, erythema and flushing were reported to return with greater severity than was present at baseline. Most of the cases were observed within the first 2 weeks of starting the treatment (see section 4.8).

Intermittent flushing occurred in some patients treated with MIRVASO topical gel.
The onset of flushing relative to application of MIRVASO topical gel varied, ranging from approximately 30 minutes to several hours (see section 4.8). **In the majority of these cases, erythema and flushing resolved after discontinuation of MIRVASO topical gel.**
In case worsening of erythema occurs, MIRVASO topical gel should be discontinued. Symptomatic measures, such as cooling, NSAID and antihistamines, may help in alleviating symptoms.

Recurrences of aggravated erythema and flushing have been reported after re-administration of MIRVASO topical gel. Prior to resuming treatment after temporary discontinuation due to aggravated erythema or flushing, perform a test application on a small area of the face for at least one day before full facial application is resumed.

It is important to inform the patient not to exceed the maximum recommended dose (5 pea sized amounts) and frequency of application: once daily use in a thin layer.

Mirvaso should not be applied close to the eyes.

Any increase in the daily amount applied and/or frequency of daily application of Mirvaso should be avoided, since the safety of higher daily doses or repeated daily application has not been assessed.

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).

Paediatric Use
The safety and efficacy of MIRVASO in children aged less than 18 years have not been established. MIRVASO should not be used in children aged less than 2 years because of serious systemic risk. Safety concerns related to systemic absorption of brimonidine have also been identified for the age group 2 to 12 years (see section 4.0).

Mirvaso should not be used in children or adolescents aged 2 to 18 years.

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.

4.5 Interaction with other medicines and other forms of interaction
No interaction studies have been performed.

Monoamine oxidase (MAO) inhibitors may interfere with the metabolism of brimonidine and potentially result in an increased systematic side-effect such as hypotension.

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 section 4.3).

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.

4.6 Fertility, Pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Overall, MIRVASO gel was shown to be well tolerated, with the most commonly (ie. ≥ 1%) reported adverse drug reactions being erythema, pruritus, flushing, rosacea 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.

No meaningful differences in the safety profiles were observed between elderly subject population and subjects 18 to 65 years of age.

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, several hours after application.

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. Aggravated erythema, flushing, skin burning

sensation and application site pallor have been reported during the post-marketing period (see section 4.4).

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

Adverse Effects
Adverse effects that occurred in at least 1% of subjects treated with MIRVASO topical gel once daily for 29 days are presented in Table 3.

Table 3: Adverse Effects 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 (%)**
Subjects with at least one adverse effect, Number (%) of Subjects	**109 (33)**	**91 (28)**
Headache	15 (5%)	12 (4%)
Erythema	12 (4%)	3 (1%)
Flushing	9 (3%)	0
Pruritus	8 (2%)	7 (2%)
Nasopharyngitis	8 (2%)	7 (2%)
Intraocular pressure increased	7 (2%)	9 (3%)
Skin burning sensation	5 (2%)	2 (1%)
Dermatitis contact	3 (1%)	1 (<1%)
Dermatitis	3 (1%)	1 (<1%)
Rosacea	3 (1%)	5 (2%)
Skin irritation	3 (1%)	5 (2%)
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 (≥ 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).

Post-marketing experience
Adverse reactions reported during post-marketing period include:

- aggravated erythema, flushing, skin burning sensation and rosacea, reported with a common frequency during post-marketing period

- swelling of the face, urticaria and dizziness, reported with an uncommon frequency during the post-marketing period

- hypotension, angioedema and bradycardia, reported with a rare frequency during the postmarketing period.

Vascular disorders: pallor or excessive whitening at the application site.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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 α_2-agonist in young children. Both children were reported to have made a full recovery within 24 hours.

Oral overdoses of other α_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 advice on the management of overdose, contact the Poison Information Centre on 0800 746766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, Other dermatologicals, ATC code: D11AX21

Brimonidine is a selective α_2-adrenergic receptor agonist that is 1000-fold more selective for the α_2-adrenergic receptor than the α_1-adrenergic receptor.

Topical facial application of a highly selective α_2-adrenergic receptor agonist is intended to reduce erythema through direct cutaneous vasoconstriction.

5.2 Pharmacokinetic properties

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 (± standard deviation) plasma maximum concentration (C_{max}) and area under the concentration- time curve from 0 to 24 hours ($AUC_{0\text{-}24hr}$) were 46 ± 62 pg/mL and 417 ± 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 25°C do not freeze.
Use within 6 months after first opening.

6.5 Nature and contents of container

2g (sample pack)
Polyethylene (PE)/Aluminium (Al)/ Polyethylene (PE) laminated plastic tubes with a high density polyethylene (HDPE) head and polypropylene (PP) closure.

10 g and 30g (trade packs)
Polyethylene (PE)/Aluminium (Al)/ Polyethylene (PE) laminated plastic tubes with a high density polyethylene (HDPE) head and polypropylene (PP) child resistant closure.

or

2g (sample pack)
Polyethylene (PE)/Copolymer/Aluminium (Al)/Copolymer/Polyethylene (PE) polyfoil plastic tubes (kind of laminate) with a high density polyethylene (HDPE) head and polyethylene (PE) child resistant closure

10 g and 30g (trade packs)
Polyethylene (PE)/Copolymer/Aluminium (Al)/Copolymer/Polyethylene (PE) polyfoil plastic tubes (kind of laminate) with a high density polyethylene (HDPE) head and polypropylene (PP) child resistant closure.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
Ph. 0800 174 104

9 DATE OF FIRST APPROVAL
12 May 2016

10 DATE OF REVISION OF THE TEXT
26 March 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Titration of dose. Facial use only
4.4	Exacerbation of rosacea symptoms Mirvaso should not be applied close to the eyes. Avoidance of dose increase.