MIRVASO® 3 mg/g gel
brimonidine

1. NAME OF THE MEDICINAL PRODUCT
Mirvaso 3 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One gram of gel contains 3.3 mg of brimonidine, equivalent to 5 mg of brimonidine tartrate.
Excipient(s) with known effect:
One gram of gel contains 1 mg methylparahydroxybenzoate (E218) and 55 mg propylene glycol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Gel.
White to light yellow opaque aqueous gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Mirvaso is indicated for the symptomatic treatment of facial erythema of rosacea in adult patients.

4.2 Posology and method of administration
Posology
One application per 24 hours, at any time suitable for the patient, for as long as facial erythema is present.
The maximum daily recommended dose is 1 g of gel in total weight, divided into five pea size amounts.
Special populations
Elderly patients
The experience of use of Mirvaso in patients aged above 65 years is limited (see also section 4.8).
Paediatric population
The safety and efficacy of Mirvaso in children and adolescents aged less than 18 years have not been established. No data are available.
Mirvaso is contraindicated in children aged less than 2 years because of serious systemic safety risk (see section 4.3). Safety concerns related to the systemic absorption of brimonidine have also been identified for the age group 2 to 12 years (see section 4.9). Mirvaso should not be used in children or adolescents aged 2 to 18 years.
Method of administration
Cutaneous use only.
Cutaneous application of a small pea size amount of medicinal product to each of the five areas of the face: forehead, chin, nose, each cheek.
Mirvaso should be applied smoothly and evenly as a thin layer across the entire face avoiding the eyes, eyelids, lips, mouth and membrane of the inner nose. Mirvaso should be applied only to the face.
Hands should be washed immediately after applying the medicinal product.
Mirvaso can be used in conjunction with other cutaneous medicinal products for the treatment of inflammatory lesions of rosacea and with cosmetics. 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 listed in section 6.1.
Children aged less than 2 years.
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 mirtazapin) antidepressants which affect noradrenergic transmission.

4.4 Special warnings and precautions for use
Mirvaso should not be applied on irritated skin (including following laser therapy) or open wounds. In case of severe irritation or contact allergy, the treatment with the medicinal product should be discontinued.
Erythema and 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).
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 recommended dose and frequency of application: once daily use in a thin layer.
Mirvaso should not be applied close to the eyes.
Mirvaso has not been studied in patients with renal or hepatic impairment.
Any increase in the daily amount applied and/or frequency of daily application of the medicinal product should be avoided, since the safety of higher daily doses or repeated daily application has not been assessed.
The concomitant use of other systemic alpha adrenergic receptor agonists may potentiate the undesirable effects of this class of medicinal products 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.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.
Mirvaso is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on tricyclic or tetracyclic antidepressants which affect noradrenergic transmission (see section 4.3).
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. Caution, however, is advised in patients taking substances which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.
Caution is advised when initiating (or changing the dose of) a concomitant systemic substance (irrespective of pharmaceutical form) which may interact with alpha adrenergic receptor agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (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
Pregnancy
There are no or limited amount of data from the use of brimonidine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Mirvaso during pregnancy.
Breast-feeding
It is unknown whether brimonidine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Mirvaso should not be used during breast-feeding.
Fertility
Brimonidine did not present any special reproductive or developmental hazard in animal species.

4.7 Effects on ability to drive and use machines
Mirvaso 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 erythema, pruritus, flushing and skin burning sensation, all occurring in 1.2 to 3.3% of patients in clinical studies. They are typically mild to moderate in severity, and usually do not require discontinuation of treatment. No meaningful differences in the safety profiles were observed between the elderly subject population and subjects 18 to 65 years of age.
Aggravated erythema, flushing and skin burning sensation have been reported during the post-marketing period (see section 4.4).
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 Mirvaso in clinical studies (see Table 1).

Table 1 – Adverse reactions

System Organ Class	Frequency	Adverse reactions
Cardiac disorders	Rare	Bradycardia*
Nervous system disorders	Uncommon	Headache, paraesthesia
Eye disorders	Uncommon	Eyelid oedema
Vascular disorders	Common	Flushing, pallor at the application site*
	Uncommon	Dizziness*
	Rare	Hypotension*
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal congestion
Gastrointestinal disorders	Uncommon	Dry mouth
Skin and subcutaneous tissue disorders	Common	Erythema, pruritus, skin burning sensation, rosacea
	Uncommon	Acne, allergic contact dermatitis, contact dermatitis, dermatitis, dry skin, pain of skin, skin discomfort, rash papular, skin irritation, skin warm, swelling face*, urticaria*
	Rare	Angiodema*
General disorders and administration site conditions	Uncommon	Feeling hot, peripheral coldness

*Adverse reactions reported from post-marketing data.

Galderma Laboratories
Product code: MOCK UP
Product description: MIRVASO GEL
Market: EX2
Article: Leaflet
Flat size: 180x315 Font size: 7 pt
Fold size: 180x26,25 Pharmacode: TBD
GRAPHIC DESIGNER: Guillaume ANDRÉ
INDUSTRIALIZATION DEPARTMENT
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GALDERMA

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PLEASE CHECK PROOF CAREFULLY TO ENSURE ALL ELEMENTS ARE CORRECT.

Description of selected adverse reactions
Bradycardia and hypotension
Post-marketing cases of bradycardia, hypotension (including orthostatic hypotension) and dizziness have been reported, some of which required hospitalization. Some cases involved application of Mirvaso following laser procedures (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
Overdoses after oral use of other alpha2-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.

No cases of overdose after cutaneous use of Mirvaso were reported during the clinical development program.

Paediatric population
Serious adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other dermatological preparations, Other dermatologicals, ATC code: D11AX21.

Mechanism of action
Brimonidine is a highly selective alpha$_2$-adrenergic receptor agonist that is 1000-fold more selective for the alpha$_2$-adrenergic receptor than the alpha$_1$-adrenergic receptor.

Pharmacodynamic effects
Cutaneous facial application of a highly selective alpha$_2$-adrenergic receptor agonist reduces erythema through direct cutaneous vasoconstriction.

Clinical efficacy and safety
The efficacy of Mirvaso in the treatment of moderate to severe facial erythema of rosacea has been demonstrated in two randomised, vehicle controlled blinded clinical trials, which were identical in design. Moderate to severe erythema was defined as a grade 3 or greater on both the Clinician Erythema Assessment (CEA) scale and Patient Self-Assessment (PSA) scale. The studies were conducted in 553 randomised subjects aged 18 years and older who were treated once daily for 4 weeks with either Mirvaso or vehicle. Of these, 539 completed 29 days of treatment and had data available to be included in the efficacy analysis at Day 29, with the majority being Caucasians between 18 and 65 years of age.

The primary endpoint was expressed in terms of composite success i.e. subjects responding with a 2-grade reduction on both baseline CEA score and baseline PSA score on Day 29. The results from both clinical studies demonstrated 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 (primary endpoint, see Table 2). For the population subset of patients with severe erythema at baseline Day 1 (i.e. subjects with CEA or PSA grade of 4) which represented 26% of the randomised subjects, the results on the primary endpoint on Day 29 were similar to those results observed in the overall population (see Table 3) and were statistically significant for both studies combined (p=0.003). In addition, for the overall population, Mirvaso demonstrated statistical superiority (p<0.001) over vehicle gel with respect to rapid initial onset of a clinically meaningful effect (1-Grade Composite Success for CEA and PSA) after the first application at 30 minutes on Day 1 (secondary endpoint 27.9% vs. 6.9% for Study 1, 28.4% vs. 4.8% for Study 2), and to achievement of a clinically meaningful effect (1-Grade Composite Success for CEA and PSA) on Day 29 (tertiary endpoint, see Table 4).

CEA and PSA were defined as follows:

CEA: Clinician Erythema Assessment: 0=Clear skin with no signs of erythema, 1=Almost clear; slight redness, 2=Mild erythema; definite redness, 3=Moderate erythema+ marked redness and 4=Severe erythema+ fiery redness

PSA: Patient Self-Assessment: 0=No redness, 1=Very mild redness, 2=Mild redness, 3=Moderate redness and 4=Severe redness

Table 2: Percentage of subjects with a 2-grade improvement in both CEA and PSA

Success day 29	Study 1		Study 2	
	Mirvaso Gel n=127	Vehicle Gel n=128	Mirvaso Gel n=142	Vehicle Gel n=142
3 hours after application	31.5%	10.9%	25.4%	9.2%
6 hours after application	30.7%	9.4%	25.4%	9.2%
9 hours after application	26.0%	10.2%	17.6%	10.6%
12 hours after application	22.8%	8.6%	21.1%	9.9%
Day 29 p-value	<0.001	-	<0.001	-

Table 3: Percentage of subjects with severe erythema at baseline Day 1 (CEA or PSA grade 4) with 2-grade improvement in both CEA and PSA

Success day 29	Study 1 + Study 2	
	Mirvaso Gel n=79	Vehicle Gel n=63
3 hours after application	22.8%	9.5%
6 hours after application	26.6%	7.9%
9 hours after application	20.3%	11.1%
12 hours after application	21.5%	4.8%
Day 29 p-value	0.003	-

Table 4: Percentage of subjects with a 1-grade improvement in both CEA and PSA

Success day 29	Study 1		Study 2	
	Mirvaso Gel n=127	Vehicle Gel n=128	Mirvaso Gel n=142	Vehicle Gel n=142
3 hours after application	70.9%	32.8%	71.1%	40.1%
6 hours after application	69.3%	32.0%	64.8%	43.0%
9 hours after application	63.8%	29.7%	66.9%	39.4%
12 hours after application	56.7%	30.5%	53.5%	40.1%
Day 29 p-value	<0.001	-	<0.001	-

No clinically meaningful trends with respect to tachyphylaxis or rebound effects (worsening of baseline erythema after cessation of treatment) were observed with use of Mirvaso for 29 days.

The results from a long term open label study in 449 patients, with continuous treatment for up to one year, confirmed that chronic use of Mirvaso is safe and effective. Daily reductions in erythema for the first month of use (as measured with the CEA and PSA scales) were similar to those observed in the controlled trials, and those reductions were achievable for up to 12 months with no apparent loss of effect over time. The overall frequencies of adverse reactions in this study are reflected in Table 1 above, with the highest rates occurring in the first 29 days of use. No adverse reactions had an increase in frequency over time, and there was no evidence that long-term use of Mirvaso conveyed an increased risk of occurrence of any specific type of adverse reaction.

Concomitant use of Mirvaso with other medicinal products for the treatment of inflammatory lesions 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 concerned subpopulation (131/449 patients in the study used concomitant rosacea medicinal product).

5.2 Pharmacokinetic properties

Absorption
The absorption of brimonidine from Mirvaso was evaluated in a clinical study in 24 adult subjects with facial erythema of rosacea. All enrolled subjects received a single-day ocular administration of a 0.2% eye drops solution of brimonidine followed by a once daily cutaneous application of Mirvaso for 29 days (intra-individual comparison of systemic exposure). On Day 1 of the study, all subjects received 1 drop of the 0.2% eye drops solution in each eye, every 8 hours over a 24-hour period (3 doses in total).

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_{0-24hr}) were 46 ± 62 pg/mL and 417 ± 264 pg.hr/mL respectively. These levels are significantly lower (2-fold) than those observed following single-day ocular administration of a 0.2% eye drops solution of brimonidine.

Distribution
The protein binding of brimonidine has not been studied.

Biotransformation
Brimonidine is extensively metabolised by the liver.

Elimination
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Carbomer
Methylparahydroxybenzoate (E218)
Phenoxyethanol
Glycerol
Titanium dioxide
Propylene glycol
Sodium hydroxide
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
This medicine should not be used after the expiry date (Exp. Date) shown on the pack.

6.4 Special precautions for storage
Do not store above 30°C.
Do not freeze.

6.5 Nature and contents of container
Polyethylene (PE)/Aluminium (Al)/ Polyethylene (PE) laminated plastic tubes with a high density polyethylene (HDPE) head and polypropylene (PP) child resistant closure.

Pack sizes: 1 tube of 2 g,10 g or 30 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

Manufactured by:
LABORATOIRES GALDERMA
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74540 Alby-sur-Chéran
FRANCE

Date of revision of the leaflet: February 2019

GALDERMA P2XXXX-X

Galderma Laboratories
Product code: MOCK UP
Product description: MIRVASO GEL
Market: EX2
Article: Leaflet
Flat size: 180x315 Font size: 7 pt
Fold size: 180x26,25 Pharmacode: TBD

GRAPHIC DESIGNER: Guillaume ANDRÉ
INDUSTRIALIZATION DEPARTMENT
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