# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

## 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 (E1520).

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, which corresponds to approximately five pea sized amounts.

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.

*Special populations*

*Elderly patients*
The experience of use of Mirvaso in patients aged above 65 years is limited (see also section 4.8). No dose adjustment is necessary.

*Hepatic and renal impairment*
Mirvaso has not been studied in patients with hepatic and renal impairment.

*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.

Mirvaso should be applied smoothly and evenly as a thin layer across the entire face (forehead, chin, nose and both cheeks) 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.

Exacerbation of rosacea symptoms is very common in patients treated with Mirvaso. Across all clinical studies, 16% of patients receiving Mirvaso experienced an event of symptom exacerbation. Treatment should be initiated with a small amount of gel and the dose increased gradually, based on tolerability and response to treatment (see section 4.2).

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 maximum dose (5 pea size amounts) and frequency of application (once daily).

Mirvaso should not be applied close to the eyes.

Concomitant use of other systemic alpha adrenergic receptor agonists
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.

Other
Any increase in the daily amount applied above 5 pea sized amounts and/or increase in 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.

One gram of gel contains 1 mg methylparahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed). This medicine also contains 55 mg propylene glycol (E1520) in each gram which is equivalent to 5.5% w/w, it 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. 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 either in clinical studies, or during the post-marketing experience (identified by an asterix (*) in 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, rosacea, skin burning sensation |
| | 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 | Angioedema* |
| General disorders and administration site conditions | Uncommon | Feeling hot, peripheral coldness |

* Adverse reactions reported from post-marketing data.

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 hospitalisation. Some cases involved application of Mirvaso following laser procedures (see section 4.4).

Other special populations
*Elderly patients*

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

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 listed in Appendix V.

## 4.9 Overdose

Overdoses after oral use 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.

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).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Mirvaso in all subsets of the paediatric population in treatment of rosacea (see section 4.2 for information on paediatric use).

## 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 (E1520)
Sodium hydroxide
Purified water

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Store below 30°C and do not freeze.

### 6.5 Nature and contents of container

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

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

And

Polyethylene (PE)/ Polyethylene (PE)/Copolymer/Aluminium (Al)/Polyethylene (PE)/Polyethylene high density (PEHD) and Linear low density polyethylene (LLDPE) polyfoil tubes with polypropylene (PP) child resistant closure.

Pump of 30 g
Multidose container with airless pump system with child resistant closure.
Polypropylene (PP) / Thermoplastic Polyolefin (TPO) / high density polyethylene (HDPE) and polypropylene (PP) child resistant closure.

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

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Galderma International
Tour Europlaza, 20 avenue André Prothin – La Défense 4
La Défense Cedex 92927
France

## 8. MARKETING AUTHORISATION NUMBER(S)

Polyethylene (PE)/Copolymer/Aluminium (Al)/Copolymer/Polyethylene (PE) polyfoil tubes:
EU/1/13/904/004
EU/1/13/904/005
EU/1/13/904/006

Polyethylene (PE)/ Polyethylene (PE)/Copolymer/Aluminium (Al)/Polyethylene (PE)/Polyethylene high density (PEHD) and Linear low density polyethylene (LLDPE) polyfoil tubes:
EU/1/13/904/008
EU/1/13/904/009

Polypropylene (PP) / Thermoplastic Polyolefin (TPO) / high density polyethylene (HDPE) and polypropylene (PP) child resistant closure.
EU/1/13/904/007

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2014
Date of latest renewal: 22 November 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Laboratoires Galderma
Z.I. Montdésir
74540 Alby-sur-Chéran
France

And

Galderma Laboratorium GmbH
Toulouser Allee 19a-23a,
Pempelfort,
Duesseldorf,
North Rhine-Westphalia,
40211,
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequently updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Mirvaso 3 mg/g gel
brimonidine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of gel contains 3.3 mg of brimonidine.

## 3. LIST OF EXCIPIENTS

Excipients: Carbomer, methylparahydroxybenzoate (E218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol (E1520), sodium hydroxide, purified water. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gel
2g
10 g
30 g

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not swallow.
Read the package leaflet before use.
Cutaneous use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 30°C and do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Galderma International
Tour Europlaza, 20 avenue André Prothin
La Défense 4
92927 La Défense Cedex
France

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/904/004
EU/1/13/904/005
EU/1/13/904/006
EU/1/13/904/007
EU/1/13/904/008
EU/1/13/904/009

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Mirvaso

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**30 G TUBE / MULTIDOSE CONTAINER WITH AIRLESS PUMP**

## 1. NAME OF THE MEDICINAL PRODUCT

Mirvaso 3 mg/g gel
brimonidine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of gel contains 3.3 mg of brimonidine.

## 3. LIST OF EXCIPIENTS

Excipients: Carbomer, methylparahydroxybenzoate (E218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol (E1520), sodium hydroxide, purified water. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Gel
30 g

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not swallow.
Read the package leaflet before use.
Cutaneous use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 30°C and do not freeze

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/13/904/006
EU/1/13/904/007
EU/1/13/904/009

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**10 G TUBE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mirvaso 3 mg/g gel
brimonidine
Cutaneous use.

## 2. METHOD OF ADMINISTRATION

Do not swallow.
Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

## 6. OTHER

Keep out of the sight and reach of children.

Excipients: Carbomer, methylparahydroxybenzoate (E218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol (E1520), sodium hydroxide, purified water.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**2 G TUBE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mirvaso 3 mg/g gel
brimonidine
Cutaneous use.

## 2. METHOD OF ADMINISTRATION

Do not swallow.
Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 g

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Mirvaso 3 mg/g gel**
brimonidine

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Mirvaso is and what it is used for

Mirvaso contains the active substance brimonidine which belongs to a group of medicines commonly referred to as “alpha agonists”.

It is applied to the skin of the face to treat redness due to rosacea in adult patients.

Redness of the face due to rosacea is caused by high levels of blood flow in the facial skin, which is the result of enlargement (dilation) of the small blood vessels of the skin.

When applied, Mirvaso acts to narrow these blood vessels again which reduces the excess blood flow and redness.

## 2. What you need to know before you use Mirvaso

**Do not use Mirvaso:**
- if you are allergic to brimonidine or any of the other ingredients of this medicine (listed in section 6).
- in children below 2 years of age, as they may be at greater risk of side effects from any of the medicine absorbed through the skin.
- if you are taking certain medicines used for depression or Parkinson’s disease including so-called monoamine oxidase (MAO) inhibitors (for example selegiline or moclobemide) or tricyclic antidepressants (such as imipramine) or tetracyclic antidepressants (such as maprotiline, mianserin or mirtazapin). Use of Mirvaso when taking these medicines may result in a fall in blood pressure.

**Warnings and precautions**

Talk to your doctor or pharmacist, before using Mirvaso especially if:
- the skin of your face is irritated or has open wounds.
- you have problems with your heart or your blood circulation.

- you have depression, decreased blood flow to the brain or the heart, fall in blood pressure on standing up, decreased blood flow to the hands, feet or skin, or Sjögren's syndrome (a chronic disease in which the body's natural defence - the immune system - attacks the moisture-producing glands).
- you have kidney or liver problems or have had them in the past.
- you have had, or plan to have any laser procedure on the skin of your face.

It is important to start treatment with a small amount of gel, increase the dose gradually but do not exceed the maximum dose of 1 gram (approximately 5 pea sized amounts). See also instructions 'How to use Mirvaso'.

Do not apply Mirvaso more than once a day and do not exceed the maximum daily dose of 1gram (approximately 5 pea sized amounts). See also instructions 'How to use Mirvaso'.

Worsening of skin redness, flushing or burning feeling of the skin
Up to 1 in 6 patients experience the return of their redness worse than it was initially. Such worsening of redness usually develops within the first 2 weeks of treatment with Mirvaso. Generally, it resolves spontaneously after treatment is stopped. The effect should gradually disappear within a few days in most cases. Before you restart the treatment with Mirvaso, test it on a small area of the face on a day when you can stay at home. If you do not experience worsening of redness or burning, continue with the usual treatment (see section 3).
In case of worsening or unexpected redness, discontinue the treatment and contact your doctor.

If any of the above applies to you, talk to your doctor since this medicine may not be suitable for you.

**Children and adolescents**
Do not give this medicine to children and adolescents under the age of 18 years because the safety and efficacy has not been established for this age group. This is particularly important in children under the age of 2 years (see 'Do not use Mirvaso').

**Other medicines and Mirvaso**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, because these medicines could affect your treatment with Mirvaso or Mirvaso could affect your treatment with these medicines.

Do not take Mirvaso with selegiline, moclobemide, imipramine, mianserin, or maprotiline, which are medicines that can be used for depression or Parkinson's disease, as this could lead to a change in the effectiveness of Mirvaso or could increase the chances for side effects such as a fall in blood pressure (see under 'Do not use Mirvaso').

Also, tell your doctor if you are taking any of the following medicines:
- medicines used for the treatment of pain, sleep disorders, or anxiety disorders
- medicines used for the treatment of psychiatric disorders (chlorpromazine) or used for hyperactivity (methylphenidate) or used for high blood pressure (reserpine).
- medicines which act on the same body mechanism as Mirvaso (other alpha agonists, e.g. clonidine; so-called alpha blockers or alpha antagonists, e.g. prazosin, isoprenaline which are most often used for treatment of high blood pressure, slow heart rate or asthma).
- cardiac glycosides (e.g. digoxin), used to treat heart problems.
- blood pressure lowering medicine such as beta-blockers or calcium channel blockers (e.g. propranolol, amlodipine).

If any of the above applies to you, or if you are unsure, talk to your doctor.

**Mirvaso with alcohol**
Tell your doctor if you consume alcohol regularly as this could affect your treatment with this medicine.

**Pregnancy and breast-feeding**
The use of Mirvaso is not recommended during pregnancy. This is because its effects on your unborn baby are unknown. You should not use this medicine during breast-feeding, as it is unknown whether this medicine passes into the breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

**Driving and using machines**
Mirvaso has no significant influence on the ability to drive and use machines.

**Mirvaso contains Methylparahydroxybenzoate (E218)** which may cause allergic reactions (possibly delayed). **This medicine also contains 55 mg propylene glycol (E1520)** in each gram which is equivalent to 5.5% w/w, it may cause skin irritation.

## 3. How to use Mirvaso

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

**Important:** Mirvaso is intended for adults and only for use on the skin of the face. Do not use this medicine on other parts of your body, especially moist body surfaces, e.g. your eyes, mouth, nose or vagina.
Do not swallow.
Keep Mirvaso gel away from children.

**How to use Mirvaso**
Mirvaso is recommended to be applied to the face once a day only.

During the first week, start the treatment with a small amount of gel (a pea-sized amount) as explained by your doctor or nurse.

If your symptoms remain the same or improve only slightly, you may then gradually increase the amount of gel. Spread it smoothly and evenly as a very thin layer as directed by your doctor or nurse. It is important not to exceed the maximum daily dose of 1gram (5 pea sized amounts applied to the whole face).

You should wash your hands immediately after applying this medicine.

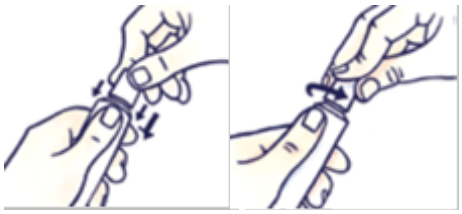
If your symptoms worsen during treatment with Mirvaso (increased redness, or burning), stop treatment and make an appointment to see your doctor – see also section 2 under `Warnings and precautions'.

You must avoid the eyes, eyelids, lips, mouth, and the inside of the nose. Should any gel get onto these areas, wash them immediately with plenty of water. If you experience worsening of redness or burning you should stop using Mirvaso and contact your doctor if needed.

Do not apply any other skin medicines or cosmetics immediately before the daily application of Mirvaso. You should use these products only after the applied Mirvaso has dried.

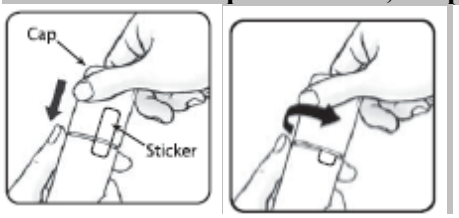
Pay attention when opening the tube / pump for the first time, not to spill a larger quantity of gel than what is needed. If this occurs, you should discard the excess gel so as not to apply more than the recommended dose. See paragraph "How to use Mirvaso" above.

[EU/1/13/904/004-006, EU/1/13/904/008-009]
**How to open the tube with a child-resistant cap**
To avoid spilling, do not squeeze the tube while opening or closing.
Push down on the cap and turn counterclockwise (turn to the left). Then pull the cap off.



**How to close the tube with a child-resistant cap**
Push down and turn clockwise (turn to the right).

[EU/1/13/904/007]
**How to open the pump with a child-resistant cap**
Push down on the cap and turn counterclockwise (turn to the left) until the cap can be removed.
**Note: when the cap is removed, the pump is not child-resistant.**




Before the first use, prime the pump by pressing down several times until the medicine is idispensed onto your fingertip.
To apply Mirvaso gel to your face, dispense a pea-sized amount of Mirvaso from the pump onto your fingertip. Continue to press down the pump to get the number of pea sizes you need according to your doctor’s prescription (but no more than 5 pea sizes in total).


To close the 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.

**If you use more Mirvaso than you should**
If you use more than the maximum daily dose of 1 gram within a 24 hour period, it could lead to skin irritation or other side effects at the application site. Repeated doses within the same 24 hour period could result in side effects, such as low blood pressure, drowsiness or sleepiness.
Please contact your doctor, who will advise you on what action to take.

**If anyone, especially a child, accidentally swallows Mirvaso, they may have serious side effects and need to be treated in a hospital.**
Contact your doctor immediately or go to a hospital emergency department right away if you, a child, or anyone else swallows this medicine and has any of these symptoms: feeling dizzy from low blood pressure, vomiting, tiredness or drowsiness, decreased or irregular heartbeats, small pupils (constricted pupils), difficult or slow breathing, floppiness, low body temperature and convulsions (fits). Take the medicine pack with you, so the doctor knows what was swallowed.

**If you forget to use Mirvaso**
Mirvaso works on a daily basis, starting with the first day of treatment. If you miss a daily dose, your redness will not be reduced for that day. Do not use a double dose to make up for a forgotten dose and continue your treatment as prescribed.

**If you stop using Mirvaso**
A potential consequence of stopping the treatment before finishing the course of treatment is the disease to come back to its initial state. Please contact your doctor before stopping your treatment, so that he could advice a replacement treatment as appropriate.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you develop uncommon side effects of severe skin irritation or inflammation, skin rash, skin pain or discomfort, dry skin, warm skin sensation, tingling or sensation of pins and needles or swelling of the face or common side effects like worsening of rosacea, discontinue the treatment and talk to your doctor since this medicine may not be suitable for you. In some cases, symptoms may extend beyond the treatment area. See also section 2 under ‘Warnings and precautions’.

If you develop contact allergy (e.g. allergic reaction, rash) or rare angioedema (a serious allergic reaction see rarely usually with swelling of the face, mouth or tongue), stop using Mirvaso and seek prompt medical advice.
Mirvaso may also cause the following other side effects:

Common side effects (may affect up to 1 in 10 people):
- flushing
- excessive whitening (pallor) where the gel is applied
- skin redness, burning feeling of the skin or itching

Uncommon side effects (may affect up to 1 in 100 people):
- acne
- dry mouth
- feeling cold in hands and feet
- feeling hot
- headache
- nasal congestion
- swelling of the eyelid
- urticaria
- dizziness

Rare side effects (may affect up to 1 in 1000 people):
- hypotension (blood pressure decreased)
- heart rate decrease (slow heart rate, known as bradycardia).

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Mirvaso

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton, tube and pump after EXP. The expiry date refers to the last day of that month.

Store below 30°C and do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Mirvaso contains**
- The active substance is brimonidine. One gram of gel contains 3.3 mg of brimonidine, equivalent to 5 mg of brimonidine tartrate.
- The other ingredients are carbomer, methylparahydroxybenzoate (E218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol (E1520), sodium hydroxide, purified water. See end of section 2 for information on methylparahydroxybenzoate and propylene glycol.

**What Mirvaso looks like and contents of the pack**
Mirvaso is a white to light yellow, opaque gel. It is supplied in tubes containing 2, 10 or 30 grams of gel or in airless pump system containing 30 g of gel.

Pack size of 1 tube or 1 pump.
Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.