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# Summary of the risk management plan (RMP) for Mirvaso (brimonidine tartrate)

This is a summary of the risk management plan (RMP) for Mirvaso, which details the measures to be taken in order to ensure that Mirvaso is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Mirvaso, which can be found on Mirvaso's EPAR page.

## Overview of disease epidemiology

Mirvaso is a treatment for erythema associated with rosacea, one of the most common long-term skin conditions, which produces redness of the face, flushing, abnormal visible blood vessels and sometimes pimples or infected red lumps. There may be burning, stinging and swelling of the face. Rosacea can also affect other parts of the body.

Rosacea affects between 1 and 20 out of 100 people in the European population, mainly between the ages of 30 and 60 years and is very rare in children. It affects both men and women but is more common in women. However, men tend to suffer complicated forms of the disease sometimes associated with facial disfigurement. It occurs mainly in people who are fair skinned.

Although the condition is not life threatening, because it affects the appearance of the face, many patients sense that the disease affects their social life with an impact on quality of life and it may be associated with depression.

The condition is often worsened by factors like sunlight, strong wind, alcohol, coffee, spicy food, exercise, stress and some cosmetics.

## Summary of treatment benefits

The effect of Mirvaso gel applied once a day to affected parts of the face over a 4-week period has been studied in two very similar studies which compared Mirvaso with gel containing no active product ("vehicle control"). The products were used without the doctor or patient knowing if they were using an active or non-active product (blinded study).

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In the first study, 129 patients were allocated to treatment with the active product and 131 to the non-active product; in the second study 148 patients were allocated to the active and 145 to the non-active product. These were patients with moderate to severe rosacea, but without complicated forms of the disease.

Treatment effect was measured by comparing responses to the active and non-active products using both the treating doctors' and the patients' rating of facial redness using graded assessment scales. Effects were assessed daily at several time points at the end of 4 weeks of treatment. Treatment success was defined as a 2 grade reduction in the grading scale score. Success rates were higher in patients treated with active product (between 25.4% (36 out of 142 patients, study 2) and 31.5% (40 out of 127 patients, study 1) depending on time of day) than with inactive product (9.2% (13 out of 142 patients, study 2), to 10.9% (14 out of 128 patients, study 1). The overall difference was statistically significant, i.e. highly likely to be a true difference rather than a chance finding. Patients treated with Mirvaso were between 2.95 and 3.75 times more likely to improve than patients treated with the non-active product.

## Unknowns relating to treatment benefits

In the main and supporting studies, all patients were of American, mainly white origin with moderate to severe rosacea. There is no evidence to suggest that the results would have been any different in white European patients. It is not known how effective the treatment would be in patients with complicated forms of rosacea. Although not studied, beneficial effects would be expected in patients with mild disease, although the benefits may not be so pronounced.

## Summary of safety concerns

***Important identified risks***

| Risk | What is known | Preventability |
|---|---|---|
| Accidental oral ingestion | Accidental oral ingestion of brimonidine has been reported to occur with an eye drop version of the product.<br>In the clinical studies of the gel, 2 cases of accidental oral ingestion occurred in young children. Because this can lead to large amounts of the product reaching the blood stream, this can result in effects on the heart, the brain and on breathing. | Avoidance of accidental exposure by appropriate packaging. The Mirvaso marketed product will have a child proof lock incorporated. |
| Sensitivity skin reactions to either the active product or to other components of the gel (Skin sensitisation to brimonidine or excipients) | Skin reactions suggestive of sensitivity, either to brimonidine itself or to the other components of the gel, have been observed in less than 1 in 100 subjects exposed. These were reactions such as allergic contact dermatitis localised to the area of application. | Sensitivity reactions tend to be unpredictable, and so are not preventable. However, the product should not be used by patients known to be sensitive to any of the product components. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Interference with how product works or reactions from product due to simultaneous use of other drugs, or interference with the effect of other products<br>(Drug interactions) | The active substance, brimonidine, could theoretically interfere with the actions of a number of substances such as medicines that affect the brain (sedatives, anaesthetics), medicines that lower blood pressure, or certain types of antidepressants. However, these effects depend upon how much brimonidine enters the blood stream. Brimonidine applied as a gel to the skin does not enter the blood stream to a significant degree. These theoretical interferences have not so far been seen with brimonidine gel.<br>It is likely that brimonidine gel may be used in patients who are receiving other types of rosacea treatments (e.g. antibiotics, retinoid treatments), either applied to the skin or as tablets.<br>Brimonidine has been used in patients taking these types of treatments - so far there have been no adverse consequences. |
| Severe allergic reactions affecting the body, to either the active substance or to other components of the gel<br>(Systemic allergic reactions to brimonidine or excipients) | A single patient has been reported (less than 1 in 1000 patients treated) who suffered a severe form of allergic reaction (swelling of face with hives), although it is likely that this was caused by a substance other than the brimonidine gel. It is not known if hypersensitivity reactions could progress to more severe allergic reactions. |

***Missing information***

| Risk | What is known |
|---|---|
| Use in pregnancy<br>(Exposure during pregnancy) | There is a limited amount of information from the use of brimonidine in pregnant women. Animal studies do not indicate that the product is harmful. |
| Use whilst breast feeding<br>(Exposure during lactation) | It is not known if brimonidine enters breast milk and can be transferred to a breast-fed child. |
| Use longer than one year | Brimonidine gel has been used by patients for up to about one year without any indication of specific risks associated with long-treatment durations.<br>Rosacea is potentially a life-long condition and so treatment duration in excess of one year is likely. |
| Use in patients or for conditions or with doses not yet studied<br>(Off-label use) | There is the possibility that Mirvaso could be used by patients for conditions other than rosacea that cause redness of the face (e.g. for acne), or that patients might use the cream several times during the day to enhance its effect. Although rosacea is rare in children, it is possible that teenagers may use the product for conditions other than rosacea. There is no information on the possible level of inappropriate use, or any special risks that might be associated with inappropriate use. |
| Use of product with treatments with light used for rosacea<br>(Use with laser or UV radiation) | There is limited information available to determine if Mirvaso can be effectively and safely used with treatments with light. Studies of the possibility of the skin being affected by light in conjunction with brimonidine (photosensitivity studies) do not |

| Risk | What is known |
|---|---|
| | indicate that any specific problems would be anticipated. |
| Use in patients who have significant additional diseases<br>(Use in patients with intercurrent disease) | The active substance, brimonidine, acts on blood vessels and could theoretically cause worsening of conditions which affect blood vessels.<br>Additionally, it is not known if patients with decreased kidney or liver function associated with other diseases who use brimonidine might be at any increased risks from treatment.<br>However, these effects depend upon how much brimonidine enters the blood stream. Brimonidine applied as a gel to the skin does not enter the blood stream to a significant degree.<br>These theoretical possibilities have not so far been seen with brimonidine gel. |

## Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Mirvaso can be found on Mirvaso's EPAR page.

This medicine has no additional risk minimisation measures.

## Planned post-authorisation development plan

***List of studies in post-authorisation development plan***

| Study / activity (including study number) | Objectives | Safety concerns / efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| RD.03.SPR 40174 Phase III Efficacy and safety Double-blind, vehicle controlled, parallel group study | To demonstrate efficacy and to assess the safety of CD07805/47 gel 0.5%, applied topically once daily for 29 days versus vehicle control, in subjects with moderate to severe facial erythema of rosacea. | None. Confirmation of efficacy and safety. | Ongoing | Final report due for completion: 08 Apr-2014 |
| RD.03.SPR 40191 Phase III Efficacy and safety Double-blind, | To demonstrate efficacy and to assess the safety of | None. Confirmation of efficacy and safety. | Planned | Final report due for completion: 17-Mar-2015 |

| Study / activity (including study number) | Objectives | Safety concerns / efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| vehicle controlled, parallel group study | CD07805/47 gel 0.5%, applied topically once daily for 29 days versus vehicle control, in subjects with moderate to severe chronic persistent vascular facial erythema. | | | |

***Studies which are a condition of the marketing authorisation***

There are no studies which are a condition of the marketing authorisation.

## Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 01-2014.