VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Soolantra® is a cream intended for the cutaneous treatment of inflammatory lesions of rosacea. Rosacea is one of the most common chronic skin conditions, characterized by erythema, flushing, abnormal visible blood vessels and sometimes pimples or infected red lumps on the face. Burning, stinging and swelling of the face might occur.

Rosacea affects between 1 and 20 out of 100 people in the population (approximately 14 million American patients suffer from this condition), mainly between the ages of 30 and 60 years; it is very rare disease in children. It affects both men and women, but it is more common in women. However, men tend to suffer from complicated forms of the disease, sometimes associated with facial disfiguration (phymas). It occurs mainly in people with fair skin.

Although the condition is not life threatening, because it affects the face many patients consider that the disease impacts their social life and quality of life. Such a condition could lead to depression.

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

VI.2.2 Summary of treatment benefits

The beneficial effect of Soolantra 1% cream has been observed in two identical clinical studies conducted in the USA and Canada. In total, 1371 subjects were allocated randomly to either Soolantra 1% Cream or a dummy medication which contained only the cream constituents (vehicle cream) without the active ingredient (ivermectin). In order to assess the efficacy of Soolantra 1% cream, treatments were applied once daily for 12 weeks. Beneficial effects were measured using an Investigator Global Assessment scale, which ranged from a score 0 (Clear - No inflammatory lesions present, no erythema) to a score 4 (Severe – Numerous small and/or large papules/pustules, severe erythema,). Assessment was also performed by counting the number of inflammatory lesions (papules and pustules) observed on the face.

Per protocol at the start of the study, all patients had a score of 3 or 4. After 12 weeks of treatment, 173 of 451 subjects (38%) treated with Soolantra 1% cream achieved a success in the first study compared to 27 of 232 (12%) treated with the vehicle cream. The mean number of inflammatory lesions reduced from 31 to 11 with Soolantra 1% cream and from 30 to 18 with the vehicle cream. Results from the second study were similar with 184 of 459 subjects (40%) achieving a success with Soolantra 1% cream compared to 43 of 229 (19%) with the vehicle cream; the number of inflammatory lesions reducing from 33 to 11 and 32 to 19 for Soolantra 1% cream and vehicle cream respectively.

Treatment with Soolantra 1% cream was continued for a further 40 weeks in both studies and showed that the number of successfully treated subjects continued to increase. After a total of 52 weeks treatment, success rates in the groups of subjects treated with Soolantra 1% cream were 71% and 76% in the two studies.

The effect of Soolantra 1% cream was also assessed compared to a marketed cutaneous treatment of rosacea (metronidazole 0.75% cream) in an additional clinical study. Nine hundred and sixty two subjects (962) were treated for 16 weeks with Soolantra 1% cream or metronidazole 0.75% cream. In the group of subjects treated with Soolantra 1% cream, a higher decrease in the mean percent change in inflammatory lesions from baseline to week 16 was observed compared to the subjects in the metronidazole 0.75% cream group (83% versus 74% respectively).

VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies, most subjects were of white/caucasian origin with moderate to severe rosacea. There is no evidence to suggest that the results would have been any different in other ethnicities, although rosacea mainly occurs in white subjects. It is not known how effective the treatment would be in subjects with complicated forms of rosacea. Although not studied, treatment beneficial effects would be expected in subjects with mild disease. Experience and safety in subjects exposed for very long periods (more than one year) is limited.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity- Contact dermatitis (allergic or irritant)	Clinical trials: 3 subjects out of more than 2000 included in clinical studies reported adverse reactions suggestive of a localised skin allergy, although it was not completely known if these were definitely due to Soolantra Cream. Animal studies suggest that the active ingredient, Ivermectin, has a low likelihood of causing allergic reactions Post-marketing experience: 47 cases reported diagnosis terms of dermatitis allergic, dermatitis contact, hypersensitivity, eczema, application site eczema, urticaria. 1 case with positive patch test to parabens. 66 additional cases with symptoms which can be suggestive of allergy including 15 cases associating several symptoms.	The information about this risk is included in sections 4.3, 4.4, and 4.8 of the product labelling. Skin sensitization is idiosyncratic and unpredictable and therefore not preventable. Identification and withdrawal of the “trigger” medication is required to prevent worsening of the reaction and for any potential of progression to system hypersensitivity.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Systemic Allergic reactions	No case observed in clinical program. One serious case and 10 non-serious cases in post marketing. Out of 237 cases from post-marketing experience and 13 cases from clinical trials regarding hypersensitivity, only one case was reported with a clear diagnosis of anaphylactic reaction, serious and medically confirmed, but no patch test performed to confirm the allergy to the ingredients of the product. It is maintain as an important potential risk to be closely monitored. Hypersensitivity is already described in the labeling of the product in the section "Contraindications".
Accidental oral ingestion	All medications intended for external use have the potential to be accidentally ingested, particularly by children. For Soolantra, the product is protected by a Child Proof Lock to minimise this risk. Ivermectin has been used as an oral medication. Whilst it is unlikely that oral ingestion of the cream would result in harm, there is limited information available at the present time. Up to now, in clinical trials one patient accidentally ingested the product but no adverse events were reported, except for bad taste on the mouth. In post-marketing, two cases were reported without adverse events associated to the ingestion of the product. Accidental oral ingestion is maintained as an important potential risk to be closely monitored, even if up to know, no safety concern has been identified after the analysis of safety data.

Missing information

Risk	What is known
Use in pregnancy *[Exposure during pregnancy]*	Studies in animals have shown that ivermectin does have toxic effects if used during pregnancy, although these effects have only been seen at doses greatly above those anticipated to be used as a cream. There are published reports of ivermectin used as an oral medication in pregnancy which do not suggest that there is any particular risk of harm. A total of 17 pregnancies have occurred in patients treated with Soolantra® in clinical studies and so experience in pregnancy is limited. In post-marketing, 2 pregnancies were reported.
Use whilst breast feeding *[Exposure during lactation]*	Studies in animals show that ivermectin is present in breast milk; it is also known that following oral use, ivermectin is present in human milk in small amounts. One case of breasfeeding was reported while applying ivermectin. No adverse reactions were reported in this case.
Use longer than one year	Rosacea is a life-long condition and effective treatment is likely to be used long-term. In Clinical studies most patients used Soolantra for up to about 1 year; experience of treatment beyond one year is limited to about 250 patients. No particular safety issues are expected to occur during long-term treatment with Soolantra. In post-marketing, one case was reported to be treated for more than 1 year. Labelled adverse reactions appeared to this patient. No special risk has been identified.
Use in patients or for conditions not yet studied *[Off-label use]*	There is the possibility that Soolantra could be used by patients for conditions other than rosacea that cause redness of the face (e.g. for acne). Although rosacea is rare in children, it is possible that teenagers may use the product for conditions other than rosacea. Up to now, the adverse reactions reported in association with misuse/off-label/medication error use are various but suggestive of inflammation, irritation or hypersensitivity, which are similar to those reported in the approved indication. No safety concern has been identified from cases reported of misuse and off-label use. The missing information off-label use will be closely monitored.
Use with concomitant topical therapies	There is no information available to determine if Soolantra ca be effectively and safetly used with concomitant topical therapies for rosacea treatment. There is one Phase 4 study where ivermectine was studies with brimonidine; no safety concern was raised from this study. Nevertheless, use of Soolantra with other concomitant topical therapies for rosacea treatment will be closely monitored.
Use of product with "light treatments" used for rosacea *[Use with laser or UV radiation]*	There is no information available to determine if Soolantra can be effectively and safely used with light treatments. Studies of the possibility of skin being affected by light in conjunction with Soolantra do not indicate that any specific problems would be anticipated. In post-marketing, the adverse reactions reported while patients were exposed to sun are suggestive of irritation which is listed with the product or rosacea which is the treated disease. No new safety concern has been identified. The few cases reporting concomitant sun exposure or use of laser therapy did not show any specific interaction between ivermectin and sun exposure or laser treatment.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language for patients is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Soolantra 1% cream can be found in the Soolantra EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

The major changes to the Risk Management Plan over time are showed below:

Version	Date	Safety Concerns	Comment
v.1.1	26 Nov 2016	Contact dermatitis (allergic or irritant)	It has been upgraded from Important Potential Risk to Important Identified Risk Dermatitis contact and dermatitis allergic have been added to the Product Information
v.1.1	01 Dec 2016	Systemic Allergic Reactions	Important Potential Risk: PRAC requested to further investigate this events (PSUSA/00010376/201604)
v. 1.1	25 Oct 2016	Targeted Questionnaire for cases of Aggravation of rosacea	Open signal discussed within PSUSA PSUSA/00010376/201604 to be closely monitored
V 1.2	02 Oct 2017	Targeted Questionnaire for cases of Aggravation of rosacea	Deletion from Annex 7 of this questionnaire. Aggravation of rosacea is not a safety concern.
V 1.2	02 Oct 2017	Missing Information: Use with concomitant topical therapies	This safety concern have been corrected and added to the missing information. It will be closely monitored with routine PV activities