VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acne vulgaris is one of the most common dermatological diseases. It affects an estimated 85% of teenagers and often continues into adulthood. Although onset of acne normally begins in adolescence, it is not uncommon for individuals to experience their first symptoms after puberty, with 30-40% of cases reportedly occurring between the ages of 35–45 [3-4]. Acne affects approximately 650 million people throughout the world, or nearly 1 in every 10 people.[5] Recently, data have shown that acne is increasing in younger population. A study in Lithuanian population has shown that acne can start as early as 7 years old.

VI.2.2 Summary of treatment benefits

The efficacy of Epiduo® Gel applied once daily for the treatment of *acne vulgaris* was assessed in two 12-week, multicenter, controlled clinical studies of similar design, comparing Epiduo® to its individual active components, adapalene and benzoyl peroxide, and to the gel vehicle in 1686 3338 acne included in each of these 2 studies. Overall, the net beneficial effect (active minus vehicle) obtained from Epiduo® was greater than the sum of the net benefits obtained from the individual components, thus indicating a potentiation of the therapeutic activities of these substances when used in a fixed-dose combination. An early treatment effect of Epiduo® was consistently observed for Inflammatory Lesions (papules and pustules) at the 1st week of treatment. Non-inflammatory lesions (open and closed comedones) responded between the first and fourth week of treatment. The benefit on inflammatory and non-inflammatory lesions in acne has been established.

The efficacy of Epiduo Forte (adapalene 0.3%/BPO 2.5%), has also been demonstrated in a clinical study conducted in 503 subjects with moderate to severe acne.

Epiduo can be also used as a long-term therapy, because neither adapalene nor benzoyl peroxide generate antibiotic resistance. Adapalene provides long-lasting benefit by controlling microcomedone formation.

In conclusion

Epiduo is a unique fixed dose combination of adapalene and BPO. It acts synergistically in patients with mild to moderate acne alone. This antibiotic free combination can be used also in association with oral antibiotics in more severe acne (as recommended by guidelines), including severe acne with nodules and can be used in the long term, as it does not contain antibiotic. Epiduo Forte® has shown clinically relevant results in patients presenting with numerous papulopustules and up to 2 nodules. Epiduo is a fixed combination product that fit acne guidelines, and can be used for short initial and long term maintenance therapy.

VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of Epiduo® in children below 9 years have not been established. This population is advised not to use Epiduo®.

The efficacy and safety of Epiduo Forte ® in children below 12 years have not been established. This population is advised not to use Epiduo Forte®.

VI.2.4 Summary of safety concerns

Table 48 Important identified risks

Risk	What is known	Preventability
None	NA	NA

Table 49 Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Teratogenicity	The active substance, adapalene belongs to a class of medicines called retinoids. Harm to developing foetuses has been demonstrated with these substances if they enter to blood circulation. The types of harm include birth defects affecting the ears, face heart and brain. The combination Adapalene/BPO, when applied to the skin does not enter the blood circulation to any significant degree and it is therefore unlikely that Epiduo or Epiduo Forte® would pose any real risk. However as a precaution, it is advised that pregnant women should not use the product. Measures are reinforced with Epiduo Forte® where women of childbearing potential should use an effective birth control method. The last review of pregnancies performed by an external teratologist expert (see Annex 12b) confirms the absence of arguments to consider Epiduo® as a teratogen or a developmental toxicant.
Serious systemic allergic reactions	The PSUR RMS assessment report of the period from September 2009 to 2010 (SE/H/664) highlighted the occurrence of allergic reactions with prominent skin symptoms which could be part of Quincke's oedema. However, given the presence of both type 1 and type 4 "typical" hypersensitivity symptoms in the cases, the diagnoses remained unclear. The MAH was recommended to add the adverse events of "throat tightness' and "eyelid oedema" to the label of Epiduo®. There was no evidence of serious potentially life-threatening reactions and the most common reaction was face/eyelid oedema and/or throat tightness which since have been listed in the reference safety information. Serious systemic allergic reactions and particularly "angioedema" continue to be closely monitored and would be added to the section 4.8 if additional cases reporting angioedema were reported.
Bullous dermatitis	The PRAC PSUR assessment report of the period from October 01st 2013 to September 2014 (PSUSA/00000059/201409) considered that the RMP shoud be updated with the important potential risk "bullous dermatitis". Based on the reporting of two respective cases of bullous dermatitis (extensive acute bullous eczema with eyelids oedema that occurred after one application of Epiduo and resolved within one week) and erythema multiforme (poorly documented), the signal on bullous dermatitis was opened on request of the PRMS. The high level of reported "blisters" or "vesicles" and "skin exfoliation" is considered as symptoms of irritation or contact allergy which are both listed with Epiduo.

Table 50 Missing information

Risk	What is known
None	NA

VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan

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

Not applicable