VI.2 Elements for a Public Summary

Epiduo® was first approved in 2007. It is a combination product associating 2 active substances with more 20 years post authorisation experience for adapalene and more than 40 years for benzoyl peroxide. The safety profile of Epiduo® can be considered to be well established with no product specific pharmacovigilance issues identified pre-or post authorisation which are not adequately covered by the current SmPCs. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are considered sufficient to identify any risk with the product.

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

Epiduo is a unique fixed dose combination of a topical retinoid (adapalene 0.1%) and benzoyl peroxide (BPO 2.5%). The fixed-dose combination has demonstrated to act synergistically in the treatment of acne, normalizing epidermal proliferation/differentiation, decreasing inflammation and stimulating innate immunity, explaining the superior clinical results seen in studies of Epiduo gel versus adapalene and BPO monotherapies in the treatment of mild to moderate acne [60-61].

Another advantage that Epiduo® is that it does not contain an antibiotic. Therefore Epiduo® does not have the potential problem of antibacterial resistance and cross-resistance that has been shown can be a problem in the long term use of antibiotics in the treatment of acne.

Epiduo can be also used as a long-term therapy, because neither adapalene nor BPO generates antibiotic resistance. Adapalene provides long-lasting benefit by controlling microcomedone formation. There is also evidence over a 1-year follow-up that shows sustained efficacy and even further improvement with Epiduo®, whereas there is no evidence of maintenance efficacy for other fixed doses combination such as for Duac® and hence it is not recommended for continuous use beyond 12 weeks.

In severe acne, Epiduo in combination with oral antibiotics (lymecycline 300mg, or doxycycline 100mg) provided significant benefit compared to doxycycline alone in a 12 week treatment. Epiduo has also been proven to be efficacious and safe as maintenance therapy in severe acne patients and also continued to reduce disease symptoms over 6 months of treatment. Epiduo Forte has been studied in patients with severe acne and has shown significant efficacy in the treatment of patients with moderate and severe acne.

As acne is a chronic disease, acute and long term therapy are needed. Epiduo is the only fixed dose combination that has been proven to be effective and safe in the short and long term use in patients with severe acne, improving adherence and patient quality of life.

Finally, as recommended by Health Authorities, oral isotretinoin should be used in Severe acne (nodular, conglobata) non responding to an appropriate treatment by systemic antibiotic and topical treatment and in certain countries like France in case of potential for permanent scarring. Epiduo was also studied in combination with 200 mg of doxycycline versus oral isotretinoin plus vehicle in severe acne with nodules and has demonstrated a better efficacy and safety profile than oral isotretinoin in a 20 weeks period. Importantly, in none of the 2 groups, there was an increase in the mean number of scars. The limitation of this study is that there is no data on maintenance therapy, nor data on relapse rates. Oral isotretinoin is still considered the only drug to “cure” the disease, even if 20-30% of cases relapse.

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 severe acne patients presenting with numerous papulopustules with or without occasional 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 a 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.
Severe cutaneous adverse reactions	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 severe cutaneous adverse reactions (SCAR) was opened on request of the PRMS. No other suspected severe cutaneous adverse reaction was reported so far. 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

No additional risk minimisation measures than recommendations presented in Summary of Product Characteristics (SmPC) and Package leaflet (PL) were considered necessary.

VI.2.6 Planned post authorisation development plan

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

Not applicable