ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION AND AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Prevora

Dental caries is a bacterial based chronic disease. The medicinal product, Prevora 100 mg/ml is a 10% w/v chlorhexidine dental solution indicated to reduce dental caries in permanent teeth of adolescents and adults. The product is a topical two-stage chlorhexidine solution. It consists of a chlorhexidine coating solution (Stage 1) and an inert sealant coating (Stage 2) which is applied after the application of the chlorhexidine solution. It is intended to be applied to the surface of permanent teeth in four weekly applications in the first month of treatment, followed by a single application at month six. Subsequent applications being based upon clinical judgment of caries risk by the dental professional.

Prevora has been evaluated in two randomised, double-blinded, placebo-controlled clinical trials (RCTs) conducted according to GCP. The two clinical studies initially submitted by the MAH to support the proposed indication were:

Clinical Study #001 (Adult Xerostomia Study)

A double-blind, randomised, multi-centred, controlled trial conducted in adults at risk of dental caries. The pivotal study included a total of 79 subjects on active.

The comparison of caries increment was active versus placebo. A 24.5% reduction for all tooth surfaces (root plus coronal surfaces) was seen with a p-value of 0.0322 [95% confidence interval (CI) of 0.62 – 0.98]. For root surfaces, a 40.8% reduction with a p-value 0.0206 (95% CI of 0.23 – 0.78) and for coronal surfaces, no significant difference was seen between placebo and Prevora (p-value 0.0644).

The results were considered not compelling enough due to the unsupportive nature of the adolescent study (below).

Clinical Study #002 (Dundee Adolescent Study)

A 3-year randomised double-blind trial in at-risk adolescent patients to evaluate the efficacy and safety of Prevora 100mg/ml Dental Solution in reducing caries increment. These were patients between the ages of 11 and 13 years with evidence of past or current caries experience and elevated levels of salivary Streptococcus mutants. This study was submitted as supportive data since it was a failed study, as no significant difference was found between placebo and Prevora as measured by the primary outcome variable. The positive results seen in this study relate only in the female subgroup which was not based on a pre-defined subgroup analysis but a post-hoc analysis. Therefore, these results do not provide robust evidence of efficacy. The objecting Member State was of the view that the evidence provided was not considered compelling enough even in the high-risk adult population. The MAH, CHX Technologies Europe Ltd submitted to CHMP for consideration the results of another study, the Prevention of Adult Caries Study (PACS), to confirm the results seen to date.

Prevention of Adult Caries Study (PACS)

This is a Phase III, multi-centre, placebo-controlled, double-blinded, prospective study. The study enrolled 983 at-risk adults and the study objectives were: determine the efficacy of Prevora in reducing cavities in at-risk adults, evaluate its safety, and evaluate the emergence if any, of chlorhexidine-resistant Streptococcus mutans post treatment in study participants, and the emergence, if any, of opportunistic infections in the form of Candida albicans post treatment in study participants.

The primary endpoint was the number of new cavities (coronal plus root surfaces) per participant, as measured at the end-of-study visit. The secondary endpoints were new coronal cavities and root cavities per participant.

The study population consisted of 983 adults ranging in age from 18 and 80 years and with a mean age of 43 years. This study population is considered representative of the patients in the EU.

As defined by the primary endpoint, this study showed no significant difference between active and placebo. Therefore, Prevora appears to have a negative effect, resulting in more cavities in the at low-risk population**.** The CHMP assessing the apparent "reverse" treatment effect for at low-risk population explained this issue by the relative absence of high risk participants (those with 3+ cavities at screening) in the placebo groups where as the high-risk population (at risk population) had a higher baseline rate of cavities.

When risk (as measured by the number of cavities at screening) is added to the ANOVA model to account for the bimodal distribution of disease in this study population at both screening and during the study, an overall clinical effect of 36.8% at $p = 0.04$ is observed. The significance of this preventive effect increases for high risk participants, for both all tooth surfaces and for coronal surfaces. There is no evidence of a difference in the point estimates for coronal and all surfaces which suggest that the results for root surfaces should be of a similar magnitude. Although the results may not be statistically significant, there was no evidence of an interaction, and thus there are sufficient statistical evidence to grant an indication for all surfaces in the high-risk population, and not just root surfaces.

Considering the resistant and opportunistic infections, this study showed no significant resistance to *Streptococcus mutans* or opportunistic infections with *Candida albicans* after treatment with Prevora over one year in adult patients.

This study did not raise any concern in terms of safety.

Benefit-risk assessment

The PACS study failed on the primary endpoint as there was no difference between active and placebo in the number of caries per patient. However, when the result in high-risk patients is considered, a significant difference is seen between active and placebo. Therefore, when considered in addition to the previously submitted data, there is now sufficient evidence to conclude that the risk-benefit is positive in the proposed indication. In addition, the new trial also suggests a benefit for coronal surfaces, and no apparent differences between root and coronal surfaces.

It was concluded that the indication in patients at high-risk should be maintained and that the result seen with coronal surfaces should also be reflected. The following indication was agreed by the CHMP:

'*Prevora 100mg/ml Dental Solution is an antiseptic solution which is applied topically to the dentition of patients for the prevention of coronal and root caries in adult patients at high-risk of dental caries (e.g. xerostomia sufferers or those with 3 or more caries at the start of the treatment plan). To be used in dental offices only by dental professionals.'*

Furthermore, it was agreed that the product information should also be amended to reflect that no significant resistance to *Streptococcus mutans* or opportunistic infections with *Candida albicans* were observed after treatment with Prevora over one year in adult patients.

Grounds for positive opinion and amendment of the summary of product characteristics and package leaflet

Whereas,

- the assessment of all available data submitted by the MAH in particular the result from the PACS in high risk patients;
- and scientific discussion within the Committee

the CHMP has recommended the granting of the marketing authorisation for which the summary of product characteristics and package leaflet are set out in Annex III for Prevora