IPAR

Public Assessment Report

Scientific discussion

IE/H/214/01/MR

Prevora 100 mg/ml Dental Solution (CHLORHEXIDINE DIACETATE)

MAH: CHX Technologies Europe Limited

This module reflects the scientific discussion for the approval of Prevora 100 mg/ml Dental Solution. The procedure was finalised at 02/03/2011. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Background Summary:

This application has been submitted in accordance with Art.8 (3) of Directive 2001/83/EC as amended. The mutual recognition procedure is used and it concerns a known active substance (chlorhexidine diacetate) and is submitted in and is hence a dossier with administrative, quality, pre-clinical and clinical data.

With Ireland as the Reference Member State, CHX Technologies Europe Limited applied for the Marketing Authorisation for Prevora 100mg/ml Dental Solution in the United Kingdom. The product was authorized in Ireland on 5th May 2006 (PA 1205/001/001).

On 24 June 2009, Prevora entered a mutual recognition procedure (MRP) with the Concerned Member States (CMS) being the United Kingdom.
Over the course of its review, the CMS raised two key issues:

(a) the acceptability of one of the two RCTs given that it was a secondary analysis of the per protocol study population, and as a consequence,
(b) a revision to the indication approved by the RMS in 2006.

Subsequently, all parties agreed to a refined indication which was "for the prevention of root caries in adults at high risk of caries (e.g. xerostomia)".
At the request of the RMS, the Applicant presented a robust justification for accepting this MR application as a one with a single pivotal study as defined in Points to consider on application with 1. Meta-analyses; 2. One pivotal study (Doc. Ref. CPMP/EWP/2330/99). The CMS was un-compelled by this justification and requested more data from an ongoing clinical trial of Prevora in the United States, and referred the MR application to the CMDh on 20 September 2009.

On 17 November 2009, the CMDh plenary session considered arguments from RMS and CMS on Prevora, and a verbal presentation from the Applicant about the compelling data of Prevora in preventing root caries. The RMS' concluding recommendation to the CMDh was that Prevora was approvable by the CMS in that:

- Prevora clearly meets all the requirements of the EU standards as per CPMP requirements for one pivotal study, for the proposed indication.

- The adolescent RCT provided important supportive information on efficacy and safety, and was not pivotal to the proposed indication. Moreover, this second RCT was successful in a per protocol analysis, an analytic approach which the RMS considers appropriate given the low retention rates in this study of high-risk adolescents in a community high school setting.

- The CMS and RMS have approved a 1% w/w chlorhexidine gel for caries prevention in xerostomic adults, without any published data from controlled studies, or with data from meta analyses in xerostomics. Moreover, the RMS takes the view that given the well-established use of chlorhexidine in dental products, the need for compelling evidence of its efficacy from a single pivotal study is not a prerequisite for approval, and similarly, given the difficulty of conducting clinical studies with dental endpoints, the Applicant has produced very compelling (and unique) evidence to approve Prevora for the proposed indication.

- The Applicant has also set the context of public health benefits of the product including the growing and substantial unmet need for root caries prevention in the U.K.

- The Applicant has also produced a well-documented argument that Prevora, as a professional product with a sustained-release delivery system of a high concentration of chlorhexidine, can take a uniquely purposeful position in caries prevention, relative to existing low-concentration chlorhexidine products which are used at home.

During the CMDh procedure, the Netherlands and Austria supported the RMS position via written comments. No other Member States submitted comments.

At the conclusion of the CMDh, the CMS maintained its position that Prevora was not approvable because:

- The application contained a single pivotal study and other evidence of efficacy was sparse.
- The evidence from the single pivotal study was not sufficiently compelling due to the unsupportive nature of the adolescent study.
- The well-established use of chlorhexidine in oral care was not applicable for the indication of caries prevention. The CMS argues that not all oral formulations of chlorhexidine have been found in published clinical studies to demonstrate efficacy in the treatment/prevention of caries.
- Another study is required to confirm the results seen to date with Prevora and such a study, called the Prevention of Adult Caries Study (PACS), is to yield results by mid 2010.

- In January 20, 2010 the CHMP had the following concerns during the Article 29(4) Referral of Council Directive 2001/83/EC, as amended, EMEA Procedure Nr: EMEA/H/A-29/1258

Summary of major issues resolved during the CMD(h) procedure between day 0 and day 60

The legal status requested is unacceptable considering this is to be administered in dental offices by dental professionals.

This issue was resolved during the procedure in line with the RMS recommendation that the issue be considered on a national basis.

Summary of the final coordination group discussion and remaining unresolved scientific issues

Following discussion at CMD(h) and consideration of the RMS proposal for agreement, the CMS was still of the opinion that the indication '**Prevention of root caries in adult patients at high-risk of dental caries**' is non-approvable and maintained its PSRPH.

The major issue on Module 5– Clinical remained unresolved.

Major issue
The study 001 is a single pivotal study and other evidence on efficacy of Prevora dental solution for this indication was considered sparse during the CMD(h) discussion. The evidence provided was not considered compelling enough even in the high-risk adult population.

In the adult xerostomia study (the pivotal study which included a total of 79 subjects on active), the primary endpoint was to evaluate caries increment over one year's period of treatment on all tooth surfaces. P-value (Prevora vs. placebo) was 0.0322. This was considered not compelling enough due to the unsupportive nature of the adolescent study.

The adolescent study submitted as a supportive study was a failed study as no significant difference was found between placebo and Prevora as measured by the primary outcome variable. The positive result seen only in the female subgroup was not based on a pre-defined subgroup analysis but a post-hoc analysis which did not provide robust evidence of efficacy.

Well established use of chlorhexidine is not applicable for this indication (prevention of caries). Not all oral formulations of chlorhexidine have been found in published clinical studies to demonstrate efficacy in the treatment/prevention of caries. Therefore efficacy of one method of application has not been found to apply to all formulations of chlorhexidine.

Another study is required to confirm the results seen to date with Prevora. There is a study “The Prevention of Adult Caries Study (PACS)” in the US with 983 at-risk adults. Results of this are due second quarter 2010.

Proposed list of questions

The MAH is requested to address the following:

i) The evidence provided is not be considered compelling enough even in the high-risk adult population and the available results of the PACS study should be submitted to CHMP for consideration.

Following assessment of the PACS study and circulation of the assessment report by the Rapporteurs Prevora was approved for the indication of "To prevent coronal and root caries in adult patients at high-risk of dental caries (e.g. xerostomia sufferers)."

II QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form, formulation, container system, etc

II.2 2.2 Drug Substance

The active substance, Chlorhexidine diacetate, is well established and it is described in the European Pharmacopoeia (Ph.Eur.), monograph 0657. The Active Substance Master File (ASMF) procedure is followed for the drug substance.

Synthesis of the drug substance has been satisfactorily described. The materials used in the synthesis of the drug substance, control of critical steps and intermediates, manufacturing process development are well described and the process has been satisfactorily evaluated.

The proposed specifications are in line with the Ph. Eur. monograph for Chlorhexidine diacetate. The active substance specification is considered adequate to control the quality and meets the current requirements. Batch analytical data demonstrating compliance with this specification have been provided.

The analytical methods used are as per the Ph. Eur. Monograph for Chlorhexidine diacetate.

The container is suitable and provides adequate protection to the active substance.

Based on the stability data presented an appropriate re-test period has been set.

II.3 Medicinal Product

Prevora 100 mg/ml Dental Solution is used as a temporary dental coating administered supragingivally by the dental professional in the dental office to the entire permanent dentition of adolescents and adults who are at risk of dental caries.

II.3.1 Composition

The drug product consists of Stage 1 Chlorhexidine coating and Stage 2 Sealant coating. Stage 2 Sealant coating, the inert, adjunctive dental coating is applied immediately after Stage 1 Chlorhexidine coating. Stage 1 chlorhexidine coating is a clear, slightly brownish solution with a characteristic odour, free of visible particulate matter and Stage 2 sealant coating is a milky-white liquid of low viscosity with a faint characteristic odour, free of visible particulate matter. Both Stage 1 and Stage 2 are packaged in 2 ml glass vials.

II.3.2 Pharmaceutical Development

The drug product was developed in the 1980s. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The formulation development and selection of excipients is satisfactorily described. The product is a dental solution and excipients used in the product were chosen on the basis that they are commonly used in conventional formulations. Based on development studies there are no compatibility issues in relation to Stage 1 Chlorhexidine coating and Stage 2 Sealant coating.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is

manufactured using conventional manufacturing techniques. The manufacturing processes for both Stage 1 Chlorhexidine coating and Stage 2 Sealant coating are well described and controlled. The manufacturing process has been validated using full scale batches. The results show good production performance throughout production. All tests meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

II.3.4 Control of Excipients

The excipients used in Stage 1 Chlorhexidine coating and Stage 2 Sealant coating are well known pharmaceutical excipients and comply with pharmacopoeial monographs. There are no novel excipients used in the manufacture of the product.

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the relevant European guidelines and the standard requirements. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

Both Stage 1 Chlorhexidine coating and Stage 2 Sealant coating are packaged in a round amber 2 ml glass vial with a threaded neck. The cap for Stage 1 Chlorhexidine coating is black and the cap for Stage 2 Sealant coating is white. The only other difference is that Stage 1 contains an aluminum foil liner while Stage 2 does not. Six Stage 1 Chlorhexidine coating vials with caps and six Stage 2 Sealant coating vials are packaged in a cardboard box. Bottle drawings and test certificates are provided. The packaging material complies with the relevant European guidelines.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC).

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Chlorhexidine diacetate 100 mg/ml Dental Solution.

III NON-CLINICAL ASPECTS

III.1 Introduction

Prevora 100mg/ml Dental Solution is applied topically (on the surfaces of the teeth) in the oral cavity and exerts its antimicrobial effect at the site of the application.

Prevora 100 mg/ml Dental Solution has a known active substance, chlorhexidine diacetate, which was first used as an anti-plaque agent in 1969[1]. Chlorhexidine has been approved in Ireland and the European Community as an active substance for use in the oral cavity as an oral rinse and oral gel. This application has been made in accordance with EEC Directive 75//318/EEC, June 1996 Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents, (CPMP/EWP/239/95 final) which provides guidance on locally acting products with a known active substance despite a change in formulation or in dosage form (such as changing non-active substances) full toxicological and clinical data are not normally necessary for a new drug application. A number of studies together with scientific and regulatory literature including a comprehensive report from the European Agency for the Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products; Chlorhexidine : Summary Report EMEA/MRL/107/96, have been used to support this application.

III.2 Pharmacology

Chlorhexidine is a cationic chlorophenyl bisbiguanide which was first used as an anti-plaque agent in 1969. There is

considerable clinical experience with chlorhexidine and the pharmacology has been extensively studied within the literature. Chlorhexidine diacetate works topically in the oral cavity to reduce total bacterial count and cariogenic bacterial counts on a temporary basis. Within the literature chlorhexidine is thought to damage the cell wall and outer membrane and promote its own uptake where it can reach its target site at the cell cytoplasmic membrane and within the cell cytoplasmic membrane and within the cell cytoplasm; however inhibition of a specific enzyme system is not considered the mode of action.
With respect to the proposed application, the conventional view is that chlorhexidine is retained on oral surfaces by binding to acid protein groups such as phosphates, sulfates and carboxy ions. A number of mechanisms for the inhibition of plaque formation have been proposed including:

- The blocking of acidic groups of salivary glycoproteins will reduce the plaque's adsorption to hydroxyapatite and the formation of the acquired pellicle.
- The ability of bacteria to bind to tooth surfaces may be reduced by the adsorption of chlorhexidine to the extracellular polysaccharides of bacterial capsules or glycocalyces.
- Chlorhexidine may compete with calcium ions for acidic agglutination factors in plaque.

III.3 Pharmacokinetics

The pharmacokinetics of chlorhexidine are considered to be known. Limited oral absorption is observed, with most chlorhexidine (non-metabolised) found in the faeces and only 0.3% found in the urine. Furthermore based on the proposed method of application and the limited release of chlorhexidine it is considered that patients would be exposed systemically to extremely low levels of chlorhexidine.

III.4 Toxicology

The toxicity of chlorhexidine is considered to be well established in the literature. Given the proposed use of the product, systemic exposure to chlorhexidine is considered to be limited with the primary concern regarding exposure to the oral cavity in particular during application. A repeat dose study performed by CHX technologies indicated there were no observed findings at doses greatly exceeding the proposed clinical dose. Based on this study together with the published literature data regarding chlorhexidine there is considered to be no concern other than observed clinical findings of sensitization.
Chlorhexidine has been used extensively as reported in the literature. There are no reports regarding reproductive toxicity. Based on the studies presented there is considered to be no reproductive toxicity findings of concern regarding Prevora 100 mg/ml**.**

III.5 Discussion on the non-clinical aspects

Chlorhexidine has been extensively used clinically for a considerable period of time in the maintenance of dental hygiene. The pharmacology, pharmacokinetics and toxicology of chlorhexidine are considered to be well established. The applicant has presented sufficient data to support this with appropriate references.
The applicant has performed a local toxicology study to examine the local effects of Prevora in a14-day study together with two in vitro studies to determine the release profile of chlorhexidine. There were no findings of concern with respect to the local toxicity study with no sign of irritation or sensitization. The lack of observed findings is unsurprising given the observed low levels of release determined in the in vitro studies over 24 hours.
Based on new HPLC methods two new impurities were identified and were found to be above the ICH qualification threshold. It is considered that the levels of the impurities are qualified based on clinical use of the products, clinical experience and negative structural alert assessment

IV CLINICAL ASPECTS

IV.1 Introduction

Prevora has been evaluated in two randomised controlled clinical trials (RCTs) conducted according to GCP. These

studies are the first reported, and to the knowledge of the RMS, remain the only placebo-based RCTs in the caries research literature on chlorhexidine. In this regard, Prevora provides the next level of evidence for chlorhexidine's use in the oral cavity.

Table 2 Prevora's Efficacy in Two Randomized, Double-blinded, Placebo-controlled, Prospective Clinical Trials

Trial	Description	Reduction of caries increment active vs. control	Statistical significance
Pivotal Phase III, Clinical Study #001 (12 month treatment and observation period)	**Medication-induced xerostomic adults (mean age of 58 years) with a history of caries & *S. mutans* ≥ 250,000 cfu/ml counts, living in 3 different cities in North America**	**Active vs. placebo Root = 40.8%**	For the root, p = 0.02 (95% CI = 23% to 78%)
Supportive Phase III, Clinical Study #002 (36 month treatment and observation period)	High-risk adolescents (history of caries + salivary *S. mutans* ≥ 250,000 cfu/ml, attending 31 high schools in Tayside, Scotland	For female per protocol participants, Active vs. Placebo = 20% Active vs. fluoride varnish = 31% Active vs. visiting the family dentist = 28%	For active vs. all control arms, p < 0.05 Success rate where cumulative net caries increment = 0 over 3 years for per protocol females, Active = 31.3% Placebo = 11.5% Fluoride varnish = 15.8% Visiting the family dentist = 10.5%

IV.2 Pharmacokinetics

Chlorhexidine binds strongly to the oral mucosa and the dentition and thus has very poor systemic absorption. No detectable blood levels of chlorhexidine have been found after oral use.

IV.3 Pharmacodynamics

Chlorhexidine is effective against a wide range of important oral microorganisms associated with dental caries. Chlorhexidine in the drug product has been found at bactericidal levels to *Streptococcus mutans* for between 24 hours and 48 hours on the surface of adult dental patients after its application, as measured by HPLC.

There have been no published reports of permanent resistance by *Streptococcus mutans* to the repeated use of chlorhexidine for up to 2 years. The cumulative monthly mean dose of chlorhexidine delivered by Prevora Stage 1 Solution is approximately equal to that of 1.0% w/w chlorhexidine dental gel and approximately half that of 0.2% w/v chlorhexidine oral rinse.

IV.4 Clinical efficacy

The Prevention of Adult Caries Study (PACS) was a Phase III, multi-centre, placebo-controlled, double-blinded, prospective study which evaluated the ability of Prevora, a topical, in-office chlorhexidine tooth coating to prevent cavities in adults.

The study enrolled 983 at-risk adults (mean age of 43 years) in four centres in the United States, and had a treatment-observation period of 13 months. It was conducted under I.N.D. #45,466 and under protocol CHX2000-01 of the U.S. Food and Drug Administration.
The study was co-sponsored by the U.S. National Institutes of Health. It was the largest controlled study of adult caries to date.

The study commenced on April 24, 2007. The last patient exited in August 31, 2009.

The study was approved by four institutional review boards and was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki

STUDY OBJECTIVES

(a) To determine the efficacy of Prevora 100 mg/ml Dental Solution in reducing cavities in at-risk adults.
(b) To evaluate the safety of Prevora 100 mg/ml Dental Solution in these same adults
(c) To 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.

Population Studied*:*

The population in this study consisted of adults aged 18 years of age and older.
Upon recruitment completion, 983 participants had been randomised.

Active Study Medication (100 mg/ml chlorhexidine diacetate Ph Eur): This group's full dentition was treated topically with Stage 1 Chlorhexidine coating followed by the inert, temporary coating called Stage 2 Sealant coating.

Placebo of the Study Medication: This group's full dentition was treated topically with the placebo of Stage 1 Chlorhexidine coating (no chlorhexidine) followed by the inert, temporary coating called Stage 2 Sealant coating at the same treatment intervals as the Active Group.

Efficacy summary

PACS is the largest controlled study of adult caries yet to be undertaken.
PACS is the second Phase III controlled study of Prevora in at-risk adults.

The first Phase III study involved older adults (mean age of 58 years) who had minimal salivary flow because of multiple medication use. Both Phase III studies followed the same treatment regimen and administered a comparable unit dose and cumulative dose of this topical, in-office dental coating over a comparable period of time.

The first study of older, medication-induced xerostomic adults has been accepted by the RMS and CMS under mutual recognition. It reported a significant preventive effect for root caries of 41% ($p = 0.02$). This preventive effect is clinically relevant because root caries is the most common form of tooth decay past the age of 60, and is without an approved preventive treatment in the EU.

PACS enrolled 983 at-risk adults at 4 study centres in the United States. (2 insured and 2 uninsured centers - included 1 public health centre)

The average age of participants was 43 years, the age range was 18 to 80, 50.1% were female, 65.7% were White, and 65.9% reported they visited the dentist at least once a year. The treatment and observation period was 13 months.

Both treatment groups (active and placebo) appear to have been balanced in terms of gender, age, number of caries and location of caries at baseline. There was slightly more numerical root caries in the placebo versus active treatment however there was no statistical differences seen between placebo and active treatment groups.

The combined preventive effect was 60% at $p = 0.006$ and the overall significance was $p = 0.0024$.
The study also yielded a significant treatment effect on the coronal surfaces of all participants and a treatment effect which approached significance for all tooth surfaces of all participants.

IV.5 Clinical safety

The mean number of treatments per active participant was (2,318/490) 4.73. Thereby, total cumulative exposure in the active group over 13 months was 219.94 mg of chlorhexidine.

It is also noted that, according to the study's procedures for recording adverse events, the same adverse events could be reported on more than one occasion by the study staff should the patient report that event on subsequent visits. Accordingly, and to be fully comprehensive, CHX has reported the adverse events in totality, including repetitive recordings of the same adverse events.

The Data Coordinating Centre excluded such repetitive recordings of the same adverse event in its tabulation of MedDRA-based adverse events.

Accordingly, there are two data sets in this Clinical Study Report: those compiled by the Sponsor and those compiled by the Data Coordinating Centre. A comparison of the two classification systems is shown in the following table.

Table 57 A comparison of the two classification systems for adverse events
- where active treatments = 2,318 and placebo treatments = 2,370 -

	CHX classification system used in the Case Report Form	MedDRA classification system prepared by the Data Coordinating Center	CHX as a % of MedDRA adverse events
Total AEs in Active	1,293	693	186.6%
Total related AEs in Active	181	115	157.4%
Total AEs in Placebo	1,436	795	180.6%
Total related AEs in Placebo	206	133	154.9%
Related AEs in Active per 100 treatments	55.8	29.2	
Related AEs in Placebo per 100 treatments	7.8	4.9	

Brief Summary of adverse events

Deaths: There were three deaths, all of which were "definitely not related" to the study medication (Table 58). Two deaths occurred in the placebo group, and one in the active group.

Serious Adverse Events: There were 4 other serious adverse events, all of which were "definitely not related" to the study (Table 58). All of these events were resolved by the conclusion of the study.

Adverse Events:

CHX methods for reporting adverse events (see introductory paragraph to Section 12.2)

There were a total of 2,741 adverse events in the study, of which 388 (14.2%) were related to the treatment (Table 59). Mild adverse events numbered 1,930 (70.4%), moderate adverse events numbered 552 (20.1%) and severe adverse events numbered 259 (9.4%). These events occurred primarily in the oral cavity (26.6%), the musculoskeletal body system (18.8%), the respiratory system (16.0%), "other" (14.0%) and the gastrointestinal body system (7.7%).

Table 59 Total adverse events, Intent-to-Treat population, active + placebo
- CHX body system -

Body System	Mild		Moderate		Severe		Total		Total
	Related	NR	Related	NR	Related	NR	Related	NR	R + NR
Allergies	1	53	0	9	0	6	1	68	69
Cardiovascular	2	72	0	23	0	5	2	100	102
CNS	9	103	5	21	3	16	17	140	157
Endocrinology	1	60	0	16	0	8	1	84	85
Gastrointestinal	7	123	4	47	2	27	13	197	210
Immunological	1	23	0	5	0	17	1	45	46
Musculoskeletal	3	307	0	154	0	52	3	513	516
Oral	269	348	25	35	24	29	318	412	730
Respiratory	16	262	4	119	1	36	21	417	438
Salivary Gland	0	4	0	0	0	0	0	4	4
Other	9	257	2	83	0	33	11	373	384
Total	318	1612	40	512	30	229	388	2353	2741

Where Related = "definitely related" + "probably related" + "possibly related" + "remotely related" + "unknown"
Where Not related = "definitely not related"

Data Coordinating Center methods for reporting adverse events (see introductory paragraph to Section 12.2)

According to the MedDRA classification system compiled by the Data Coordinating Centre, there were 1,488 adverse events or about half those reported by the CHX methods (Table 60). Of the total, 248 (16.7%) were related. Mild adverse events numbered 1,017 (68.3%), moderate adverse events numbered 304 (20.4%) and severe adverse events numbered 167 (11.2%). These events occurred primarily in MedDRA's gastrointestinal system which includes the oral cavity (21.6%), infections (21.6%), musculoskeletal (9.6%), injuries and procedural complications (8.3%) and respiratory (7.2%). (see table 60 in clinical study report for further detail).

Adverse events and relatedness to treatment.

MedDRA classification system a total of 693 events were recorded (intention to treat population).
A total of 7 serious related adverse events were recorded (2 gastrointestinal disorders, 1 Infection and infestations, 2 nervous system disorders, 2 social circumstances)

In the placebo group a total of 795 adverse events were recorded 12 severe related events were recorded (7 gastrointestinal, 2 infections and infestations, 1 nervous system, 1 respiratory, thoracic and mediastinal disorder, 1 social circumstances)

Table 63 Total adverse events by body system, Intent-to-Treat population, active group
- MedDRA body systems -

MedDRA Body System	Mild		Moderate		Severe		Total		Grand Total
	NR	Related	NR	Related	NR	Related	NR	Related	
Blood and lymphatic system disorders	2	0	0	0	0	0	2	0	2
Cardiac disorders	2	0	1	0	0	0	3	0	3
Ear and labyrinth disorders	2	0	1	0	2	0	5	0	5
Endocrine disorders	3	0	0	0	0	0	3	0	3
Eye disorders	5	1	3	0	1	0	9	1	10
Gastrointestinal disorders	62	54	12	5	12	2	86	61	147
General disorders and administration site conditions	16	1	3	0	4	0	23	1	24
Hepatobiliary disorders	1	0	0	0	0	0	1	0	1
Immune system disorders	7	0	1	0	1	0	9	0	9
Infections and infestations	102	4	26	0	21	1	149	5	154
Injury, poisoning and procedural complications	39	1	11	0	9	0	59	1	60
Investigations	7	0	1	0	0	0	8	0	8
Metabolism and nutrition disorders	7	0	2	0	1	0	10	0	10
Musculoskeletal and connective tissue disorders	39	0	18	0	5	0	62	0	62
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0	0	0	0	0	5	0	5
Nervous system disorders	21	8	1	2	6	2	28	12	40
Pregnancy, puerperium and perinatal conditions	1	0	1	0	0	0	2	0	2
Psychiatric disorders	8	0	4	0	2	0	14	0	14
Renal and urinary disorders	2	0	2	0	0	0	4	0	4
Reproductive system and breast disorders	12	0	1	0	1	0	14	0	14
Respiratory, thoracic and mediastinal disorders	19	4	9	1	4	0	32	5	37
Skin and subcutaneous tissue disorders	22	0	3	0	1	0	26	0	26
Social circumstances	0	26	0	0	0	2	0	28	28
Surgical and medical procedures	4	0	5	1	1	0	10	1	11
Vascular disorders	12	0	2	0	0	0	14	0	14
Total	400	99	107	9	71	7	578	115	693

Body system "Neoplasms benign, malignant and unspecified" includes cysts and polyps.

Note: "Related" = Study Related and is defined as "definitely", "probably", "possibly", "remotely" study-related or "unknown".

Note: "NR" = Not Study Related and is defined as "definitely not" study-related.

Table 64 Total adverse events by body system, Intent-to-Treat population, placebo group
- MedDRA body systems -

MedDRA Body System	Mild		Moderate		Severe		Total		Grand Total
	NR	Related	NR	Related	NR	Related	NR	Related	
Blood and lymphatic system disorders	3	0	0	0	0	0	3	0	3
Cardiac disorders	1	1	2	0	0	0	3	1	4
Congenital, familial and genetic disorders	0	0	2	0	0	0	2	0	2
Ear and labyrinth disorders	3	0	1	1	1	0	5	1	6
Endocrine disorders	3	0	1	0	0	0	4	0	4
Eye disorders	9	0	1	0	0	0	10	0	10
Gastrointestinal disorders	62	60	20	12	14	7	96	79	175
General disorders and administration site conditions	13	0	3	0	2	0	18	0	18
Hepatobiliary disorders	0	0	1	0	0	0	1	0	1
Immune system disorders	10	0	5	0	1	0	16	0	16
Infections and infestations	109	1	34	0	22	2	165	3	168
Injury, poisoning and procedural complications	42	0	13	1	8	0	63	1	64
Investigations	11	0	4	0	0	0	15	0	15
Metabolism and nutrition disorders	4	0	2	0	1	0	7	0	7
Musculoskeletal and connective tissue disorders	40	3	24	1	13	0	77	4	81
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0	2	0	0	0	7	0	7
Nervous system disorders	17	12	9	3	2	1	28	16	44
Pregnancy, puerperium and perinatal conditions	0	0	1	0	0	0	1	0	1
Psychiatric disorders	3	0	5	1	2	0	10	1	11
Renal and urinary disorders	5	0	1	0	2	0	8	0	8
Reproductive system and breast disorders	1	0	2	0	0	0	3	0	3
Respiratory, thoracic and mediastinal disorders	41	6	18	1	3	1	62	8	70
Skin and subcutaneous tissue disorders	22	5	5	0	4	0	31	5	36
Social circumstances	0	10	0	1	0	1	0	12	12
Surgical and medical procedures	7	2	9	0	2	0	18	2	20
Vascular disorders	7	0	2	0	0	0	9	0	9
Total	418	100	167	21	77	12	662	133	795

Body system "Neoplasms benign, malignant and unspecified" includes cysts and polyps.

Note: "Related" = Study Related and is defined as "definitely", "probably", "possibly", "remotely" study-related or "unknown".
Note: "NR" = Not Study Related and is defined as "definitely not" study-related.

Common adverse events noted in the patient information leaflet:

A comparison of common related adverse events between the active group and the placebo group according to MedDRA shows that the rate per 100 treatments in active was 3.15 or slightly higher than placebo (Table 67). Tooth discoloration and pharmaceutical product complaint (a possible surrogate for bitter taste of which there were 51 adverse events in the CHX body classification system) was higher than in the placebo group.

Table. 67 Common related adverse events in the oral cavity, active vs. placebo
- MedDRA body system -
- where active treatments = 2,318 and placebo treatments = 2,370

Common event	Active	Rate per 100 treatments	Placebo	Rate per 100 treatments
Gingival pain	13	0.56	25	1.05
Sensitivity of teeth	13	0.56	16	0.68
Tooth discoloration	6	0.26	0	0
Burning sensation	5	0.22	6	0.25
Asthma	0	0	0	0
Oral discomfort	6	0.26	8	0.33
Oral pain	2	0.09	3	0.13
Pharmaceutical product complaint	28	1.2	12	0.50
Total	73	3.15	70	2.95

Tooth discolouration and pharmaceutical product complaint were recorded more in the active treatment group versus placebo.

In conclusion, Prevora is well tolerated, without evident systemic effects or reactions, and is consistent with the use of chlorhexidine in the oral cavity but without the rate of staining of the teeth.

Safety conclusion:
Chlorhexidine is a well known active substance.
The PACS study used two classification systems for adverse events, the CHX case report forms, CHX has reported the adverse events in totality, including repetitive recordings of the same adverse events.

The Data Coordinating Center excluded such repetitive recordings of the same adverse event in its tabulation of MedDRA-based adverse events.
Therefore the total numbers of adverse events is higher in CHX data as compared with MedDRA data.
On review of safety data from MedDRA tables, it is apparent that with active treatment mild, moderate and serious adverse events did not occur at a higher frequency that placebo.
Common adverse events that occurred in the oral cavity occurred more frequency with Prevora than placebo.

The RMS concurs with the MAH assessment that Prevora is well tolerated and is consistent with the use of chlorhexidine in the oral cavity.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

V OVERALL CONCLUSIONS

Prevora's strongly significant preventive effect in these high risk patients could have a significant impact on the overall burden of this common chronic disease, and potentially on the overall cost of dental care.

Root caries has been identified by the Atherosclerosis Risk in the Community Study conducted for the U.S. National Institutes of Health, as a significant risk factor for coronary heart disease.

The primary pathogen for root caries, *Streptococcus mutans*, has been identified as the dominant microorganism in diseased arterial plaque.

Reductions in dental caries also are reflected in increased tooth retention and reduced levels of edentulism.

As the population ages and persons retain more teeth, more root surfaces become exposed and are at increased risk for

tooth decay. Therefore highlights the importance of developing strategies for preventing and controlling dental caries in older adults especially those at high risk.

The RMS recommends approval for prevora for the indication of
“To prevent coronal and root caries in adult patients at high-risk of dental caries (e.g. xerostomia sufferers).”

VI REVISION DATE

July 2011