28 April 2016
EMA/343450/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Umbipro (TM)

International non-proprietary name: chlorhexidine

Procedure No. EMEA/H/W/003799/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

4-CA	4-chloroaniline
CEP	Certificate of Suitability
CFU	Colony Forming Units
CHMP	(EU) Committee for Medicinal Products for Human Use
CHX gel	Chlorhexidine digluconate gel, 7.1% w/w (equivalent to 4% w/w chlorhexidine)
CICAD	Concise International Chemical Assessment Document
CPDB	Carcinogenic Potency Database
CPP	Critical process parameter
CQAs	Critical quality attributes
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EEA	European Economic Area
ET-50	Effective Time-50
g	Grams
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
IARC	International Agency for Research on Cancer
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
kg	Kilograms
MA	Marketing Authorisation
MIC	Minimum Inhibitory Concentration
mcg	Microgram
mcg/day	Micrograms per day
mcg/ml	Micrograms per millilitre
mg	Milligrams
mg/day	Milligrams per day
mg/kg	Milligrams per kilogram of body weight
mg/kg/day	Milligrams per kilogram of body weight per day

mg/mL	Micrograms per millilitre
mL	Millilitres
mm	Millimetres
NGT	Not greater than
NIH (US)	National Institute of Health
Nm	Nanometres
NOEL	No observed effect level
Ppm	Parts per million
QTPP	Quality target product profile
SPC	Summary of Product Characteristics
TD50	Doses giving a 50% tumour incidence equivalent to a cancer risk probability level of 1:2
TSA	Tryptone Soya Agar
WHO	World Health Organization
w/v	Weight for volume
w/w	Weight for weight

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services submitted on 7 October 2015 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Umbipro.

The eligibility by the World Health Organisation was agreed-upon on 25 July 2013.

Umbipro will exclusively be intended for markets outside the Community.

The applicant applied for the following indication: Umbipro is indicated for prophylaxis of omphalitis (infection of the umbilical cord) in newborn infants.

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21/11/2013 and 14/01/2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Salmon Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 7 October 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 24 September 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2016. By analogy to Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 11 February 2016.
- During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be

sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 February 2016.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13/04/2016.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Umbipro (TM) on 28 April 2016.

2. Scientific discussion

2.1. Introduction

The development of 7.1 % w/w chlorhexidine digluconate (CHX) in a gel formulation (equivalent to 4% w/w chlorhexidine) is a direct response to the September 2012 United Nations (UN) Commission Report on Life-saving Commodities for Women and Children, which identified chlorhexidine for newborn cord care as one of 13 life-saving commodities.

CHX Gel is intended exclusively for countries outside the European Economic Area (EEA) and is being submitted under Article 58 of Regulation (EC) 726/2004 to obtain a CHMP Scientific Opinion which would allow issuance of a certificate of pharmaceutical product (CPP) to support future filings in target markets.

The legal basis for this application refers to Article 8.3 of directive 2001/83/EC - complete dossier for known active substance, with an extensive review of non-clinical and clinical published literature relating to chlorhexidine including the reports from early toxicology studies available to GSK originally undertaken in support of the initial product licence applications.

To support this application, in vitro antibacterial equivalence (kill time and substantivity tests) and in vitro skin-irritancy studies have been conducted to bridge efficacy and safety data from published studies of chlorhexidine digluconate solution, 7.1% w/w (equivalent to 4% w/w chlorhexidine) to the GSK CHX Gel.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a gel containing chlorhexidine digluconate 7.1% w/w (equivalent to 4% w/w chlorhexidine) as active substance.

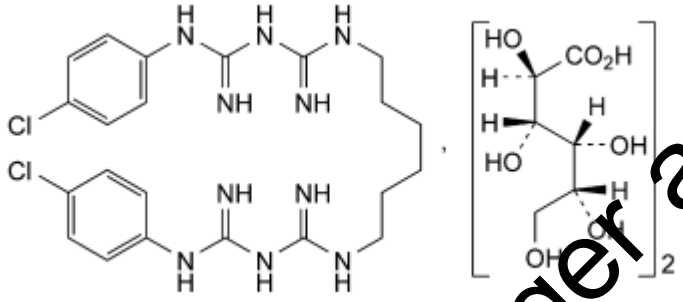
Other ingredients are: guar gum, sodium acetate trihydrate and purified water.

The product is available in a foil laminate sachet as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of chlorhexidine digluconate is N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediamidine digluconate corresponding to the molecular formula $C_{34}H_{54}Cl_2N_{10}O_{14}$ and has relative molecular mass 897.7 g/mol g/mol and it has the following structure:



As there is a monograph of chlorhexidine digluconate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The control tests comply with the specifications and test methods of the Ph Eur monograph. The active substance specification includes tests for appearance, identification, pH, relative density, related substances, impurity P, assay and methanol.

The active substance specification applied is according to the current Ph. Eur. monograph for chlorhexidine digluconate solution and includes the additional test for the residual solvent methanol by gas chromatography in accordance with the CEP. Furthermore, the active substance specification applied includes a tighter control limit for the impurity 4-chloroanaline (4-CA) as opposed to the Ph. Eur. monograph limit. 4-CA is referred to as impurity P in the Ph.Eur.

Batch analysis data for two production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

The re-test period of the substance as stated in the CEP provided by the company is 3 years if stored in HDPE drums with external metallic cover at a temperature not exceeding 25°C or 2 years if stored in HDPE drums at a temperature not exceeding 25°C. This is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Chlorhexidine Digluconate Gel, 7.1% w/w is a colourless to yellow translucent gel for topical usecontaining the equivalent of 4% w/w chlorhexidine as the free base.

The aim was to develop a product in response to the United Nations (UN) Commission Report (Sep 2012) on Life-saving Commodities for Women and Children, which identified chlorhexidine for new-born cord care as one of thirteen life-saving commodities (United Nations, 2012). The intention was to develop a gel formulation which is easier to apply than a solution and is more likely to retain the formulation at the site of application, based on the information provided in the Programme for Appropriate Technology and Health (PATH) Health Tech Report – Stability data on chlorhexidine formulations (PATH, 2010).

The development of the proposed product was guided by quality risk management (QRM) principles. The Quality Target Product Profile (QTPP) was developed to define quality characteristics of the finished product and provided the basis for the finished product design/development taking into account the PATH report/ PATH 004. The finished product Critical Quality Attributes (CQAs) were identified and an understanding of the impact of the active substance, excipients and in-process materials, as well as the parameters of the manufacturing process on finished product quality was established. Pharmaceutical development and manufacturing experience provided scientific understanding to support the control strategy during manufacture of the finished product.

The QTTP for the finished product are shown in the following table:

Dosage Form and Strength	A single unit dose topical gel, 3 g of a 7.1% w/w gel containing 213 mg of chlorhexidine digluconate drug substance, for a single application for 1 or 7 days. A low viscosity gel that is easy to apply to the affected site and able to be filled into suitable single-use containers
Drug Product Critical Quality Attributes	Description, identity, content, minimum fill, drug related impurities, 4-chloroanaline (4-CA) and pH
Drug Delivery and Release Criteria	The drug needs to be delivered topically to the surface of the skin
Container Closure System	A container closure which facilitates single dose use containing the topical gel and provides protection to the product from light and moisture egress
Stability Criteria	Components of the drug product (active and inactive ingredients) must be physically and chemically compatible with the requisite functional characteristics to ensure appropriate stability of the drug product over the shelf life of not less than 2 years under climatic zones II to IV

The finished product CQAs, input and in-process material CQAs and CPPs for chlorhexidine gel are as follows:

Type of Control	Name of Control	Cross Reference
Drug Product CQAs	Description Identity Content Minimum fill Drug related impurities 4-CA pH	N/A
Input and In-process Material CQAs	Drug Substance* Description Identity pH Content Drug-related impurities – 4-CA content Total impurities content	S.4.1. Control of Drug Substance
	In-Process Material CQAs Fill Weight Sachet Appearance Seal Integrity	P.2.3. Manufacturing Process Development, Section 5
CPPs	Gel temperature (guar gum) High shear mixing time (guar gum) Sealing temperature** Line Speed** Sealing Pressure**	P.2.3. Manufacturing Process Development, Section 5

Notes:

* Although Chlorhexidine Digluconate solution was developed before QbD principles evolved, these specification items are considered to potentially impact on patient safety and efficacy.

** These CPPs pertain to the filling process.

During development, the critical quality attributes (CQAs) of the finished product were identified. The CQAs are the attributes that were expected to have an impact on patient safety and efficacy. The designation as CQAs was confirmed as appropriate by supporting data that became available in the course of development, underpinned by risk assessment.

It was stated that the final formulation closely matches PATH 004 and has been optimised to meet the defined QTPP. The aim was to develop a low viscosity gel that is easy to apply to the affected site and able to be filled into suitable single-use containers.

The rationale for the choice of chlorhexidine as active substance was provided – high aqueous solubility, strong affinity for skin and mucous membranes, and wide, well-established use in pharmaceutical and cosmetic products, usually as a disinfectant. Furthermore, the proposed active substance complies with the Ph.Eur. monograph and is commercially available via the CEP. The active substance characteristics that impact the finished product CQAs were described and discussed.

The active substance degrades (unavoidably) via hydrolysis with multiple degradation pathways and generates a range of impurities, notably 4-chloroaniline (4-CA), which has been shown to be genotoxic and carcinogenic in non-clinical studies. The 4-CA impurity (Impurity P in the Ph.Eur. specification for chlorhexidine digluconate solution) is known to increase with time and temperature and to be impacted by pH. 4-CA content in the finished product is minimised by the following measures: controlling pH and 4-CA level in the input active substance, selection of excipients that minimise formation of 4-CA, by providing instructions on appropriate storage conditions and by testing the finished product quality against specifications for a specific pH range and 4-CA content. Data from on-going stability studies was also used to understand trends in formation of 4-CA. Taken together, this information was used to define release and shelf-life specifications for 4-CA.Therefore, the importance of pH and 4-CA contents is discussed. It is stated that the active substance stability is optimal between pH 5.5 and 7.0 and that the pH of the active substance is important to the rate of 4-CA formation, with the primary degradation mechanisms being direct formation of 4-CA from chlorhexidine under acidic conditions and indirect 4-CA formation under alkaline conditions. In order to minimise levels of 4-CA and other drug-related impurities in the finished product, the pH of the input chlorhexidine digluconate active substance is as per Ph.Eur. requirements i.e. 5.5-7.0.

Based on the scientific understanding and prior knowledge obtained from the PATH 004 formulation, excipients with appropriate functionality were assessed for the finished product in order to meet the QTPP.

In order to evaluate excipients used within PATH 004 formulation as well as additional thickening agents and pH stabilisers, binary excipient compatibility studies for chlorhexidine digluconate solution, 20% w/v were performed. Excipient compatibility studies were performed by storing binary drug-excipient mixture samples at 25°C and 40°C and testing for appearance, chlorhexidine content and total drug-related impurities including 4-CA at 2 and 4 weeks. A summary of the excipients evaluated and the amount of drug-related impurities seen over 4 week storage at 40°C has been presented. The active substance excipient ratios employed in the study were aligned to those used in the PATH 004 formulation and levels typically used in topical gels. Binary excipient compatibility studies performed as part of early formulation screening work to identify suitable excipients to use in combination with chlorhexidine digluconate solution, 20% w/v indicated that the source of guar gum may impact active substance stability. These early laboratory studies were conducted using guar gum from two different suppliers. During development, the binary mixtures were stored at 25 °C / 60% RH and 40 °C / 75% RH for up to four weeks to verify the impact of guar gum in the active substance stability . The data showed that that drug-related impurities for the mixture were not significantly different to those for the active substance alone. Based on physical and chemical attributes

observed during this testing, guar gum, sodium acetate trihydrate were deemed to be compatible with chlorhexidine digluconate solution, 20% w/v and chosen for finished product development.

Since chlorhexidine is available as a 20% w/v aqueous solution, purified water was chosen as the vehicle for formulation of the gel. Sodium acetate trihydrate was shown to result in the lowest level of drug-related impurities and was selected as the pH stabiliser. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The manufacturing process for the proposed formulation involves dissolving sodium acetate trihydrate in water, followed by dispersion and hydration of guar gum. The solution is heated at this stage to aid hydration of the guar gum. The resultant gel is then cooled to 25 °C ±2 °C followed by addition and mixing of chlorhexidine digluconate solution. The gel is subsequently deaerated using vacuum and then discharged into a holding vessel prior to being filled into foil laminate sachets using suitable form-fill seal packaging equipment.

The finished product manufacturing process has been developed utilising Quality Risk Management. In line with the principles outlined in ICH Q9, risk management has been used to support decisions regarding the manufacturing process. It has been used to direct experimental activities to further product and process knowledge and understanding, resulting in a robust manufacturing process and associated control strategy. A suitable discussion regarding the vacuum, heating/cooling rates, material addition, deaeration, and further details about the heating, holding and cooling steps were provided. This information demonstrates that sufficient controls are in place.

This risk assessment involved a detailed overview of the manufacturing process, together with prior knowledge to identify failure modes (risks) and process variables which could impact quality. These were taken into a Failure Mode and Effects Analysis (FMEA) risk assessment tool, which was used to score failure modes for severity, occurrence and detection, resulting in an overall risk score. The risks identified were then prioritised and used to inform development activities to drive process understanding and control of risks to acceptable levels. The risk management approach was also used to identify input and in process material CQAs and Critical Process Parameters (CPPs).

Risk assessments were updated during development, as knowledge increased. During these updates, risks were reviewed and parameters and material attributes reassessed. Risk assessment will continue to be used through the product lifecycle to manage risks and maintain the control strategy.

The primary packaging is foil laminate sachet. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: addition of purified water, sodium acetate trihydrate dissolution and addition, guar gum dispersion and hydration, cooling, mixing of chlorhexidine digluconate solution, deaerate, discharge, and filling and sealing. The process is considered to be a standard manufacturing process.

A Proven Acceptable Range (PAR) was established in the guar gum dispersion step (mixing time (guar gum)) and, in accordance with ICH definitions, has been determined by univariate studies for which operation within this range, while keeping other parameters constant, results in finished product meeting its CQAs relevant quality criteria. Future changes within the PARs are not anticipated to impact product quality and will be managed under the site's Pharmaceutical Quality System without regulatory action. Only a single parameter will be varied while other process parameters for a unit operation are maintained at close to target values for a change within PARs. QbD elements were used but Design Space is not claimed.

A lifecycle approach to process validation is adopted, in line with EMA 'Guideline on process validation for finished products - information and data to be provided in regulatory submissions. Process evaluation data were presented for a number of development scale and stability batches from the proposed commercial site. The presented data confirm that the manufacturing process is well controlled, robust and capable of routinely yielding product of consistent quality. The process qualification has not yet commenced;. Validation of the product manufacturing process will be conducted at the commercial site prior to market launch in accordance with an agreed validation protocol. The validation approach is designed with consideration of the CPPs and their set-points/proven acceptable range (PAR) that were identified and confirmed during process development at production scale.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), pH, apparent viscosity, minimum fill, assay (HPLC), impurities (HPLC), microbial limits (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

During the assessment, the finished product specification for 4-CA was tighten at shelf-life, but the specification limit for 4-CA at release was retained and the release and shelf-life specifications for 4-CA were discussed thoroughly. The proposed 4-CA limits were considered justified. However, the CHMP recommended reviewing the 4-CA limit for finished product at release and shelf-life once 30 commercial batches of CHX Gel have been manufactured and released.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 batches of a larger scale than the intended production scale of finished product stored under long term conditions at 30 ºC / 35% RH, and intermediate conditions at 30 ºC / 75% RH for 15 months, and also for 15 months under accelerated conditions at 40 ºC / 25% RH according to the ICH guidelines were provided. These batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Differences between the gel manufacturing process, filling and sealing process for primary stability batches and commercial site

representative batches are clearly identified and satisfactorily described. These differences are not expected to impact on product performance and quality and therefore their use in stability studies is accepted. It was also considered that the primary stability batches were manufactured according to the process representative of the commercial process.

Up to 7 months of supportive stability data on commercial scale batches were available for three batches of the finished product manufactured and packaged at the proposed manufacturing site. Stability data for the three batches stored under both long term, intermediate and accelerated conditions indicate that these batches are behaving similarly to the primary stability batches. Additionally the data demonstrate the chemical and physical stability of the finished product when stored for up to 7 months under all the conditions. Moreover, up to 18 months of supportive stability data are presented for three batches of the finished product manufactured at another manufacturing site. These batches contain the same fill as the primary stability batches, 3 g presentations in foil laminate sachets using the proposed commercial packaging material (except for one batch which was packaged in 2 g sachets). Stability data for these batches stored under long term, intermediate and accelerated conditions showed that they behave similarly to the primary stability batches, with good chemical, physical and microbiological stability of the finished product demonstrated when stored for up to 18 months at the long term stability condition.

Samples were tested for description, pH, apparent viscosity (viscometry), assay (HPLC), impurities (HPLC), and microbiological quality (Ph Eur). The analytical procedures used are stability indicating.

A slight decrease in chlorhexidine digluconate content was observed at the long term storage condition of 30 ºC / 35% RH, intermediate condition of 30 ºC / 75% RH and at the accelerated storage condition of 40 ºC / 25% RH following storage for up to 15 months. A small increase in the levels of the specified impurities was also observed at those storage conditions, with a generally faster rate of impurity formation observed at the higher temperature condition. Based on the stability data available to-date, all values are expected to comply with specifications for up to 24 months when stored under the proposed long term storage condition of 30 ºC / 35% RH in the foil laminate sachets. No significant changes were observed for apparent viscosity, pH and appearance of the finished product following storage at the long term condition of 30 ºC / 35% RH and accelerated storage condition of 40 ºC / 25 % RH for up to 15 months.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. From the literature, it is known that chlorhexidine undergoes photolytic degradation under stressed conditions when exposed to light. However the photostability studies demonstrated chemical and physical stability of the finished product when it is directly exposed to light under ICH Q1B Condition Option 2. Furthermore, the proposed primary pack is impervious to light.

The intended markets for this product, are countries in the continent of Africa and developing countries in Asia, which in terms of stability, are located in climatic zones III (hot and dry climate) and IV (IVa (hot and humid climate) and IVb (hot and very humid climate).The 'World Health Organisation (WHO) Technical Report Series, No. 953, 2009' includes recommendations for stability data which includes climate zones, III and IV (IVa and IVb). There is also guidance provided by the European Medicines Agency (EMA) on the type of stability data that is required for applications according to Article 58 of Regulation EC/726/2004 ('Quality of Medicines questions and answers: Part 2: Stability – Article-58 products'). The current storage conditions for the on-going stability studies, do cover the requirements for climatic zones III and IV (IVa & IVb), as outlined in the WHO Technical Report Series, No. 953, 2009 guideline and EMA Q&A document (on stability and Article 58 products), for semi-permeable containers.

Based on the available stability data, the proposed shelf-life of 24 months and storage conditions "Store below 30°C and away from direct sunlight" as stated in the SmPC (section 6.3) are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied some QbD principles in the development of the finished product. However, no design space is claimed for the manufacturing process of finished product.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the SOHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Reviewing the 4-CA limit for finished product at release and shelf-life once 30 commercial batches of CHX Gel have been manufactured and released.

2.3. Non-clinical aspects

2.3.1. Introduction

Many studies with chlorhexidine pre-date the introduction of the Good Laboratory Practice (GLP) regulations and the International Conference on Harmonisation (ICH) guidelines. Consequently, some nonclinical studies that would routinely be performed today were not conducted. Given the extensive clinical experience with chlorhexidine, *in vivo* nonclinical investigations have not been repeated to comply with GLP and ICH regulations.

The *in vitro* pharmacology studies and *in vitro* skin irritancy study (report 2014N213506) conducted by the Applicant have non-GLP status.

The *in vitro* skin irritancy study (report 2014N213508) conducted by the Applicant has GLP status.

2.3.2. Pharmacology

No new non-clinical primary pharmacodynamics data is presented for the indicated condition of umbilical cord infections. This is in line with previous scientific advice received by the Applicant from the CHMP (EMA/CHMP/SAWP/691170/2013). Much of the pharmacology package of the application is based on the extensive clinical experience with the active substance, chlorhexidine, which has been used in the clinical setting since the 1950s as a topical antiseptic cream for use on wounds and infections. Chlorhexidine as a positively charged molecule mediates an electrostatic interaction with negatively charged bacterial cell walls resulting in bacteriostatic and bactericidal effects. This non-specific mechanism allows for activity against a broad range of bacteria. For the current application a gel formulation of 7.1% chlorhexidine digluconate has been developed. Bridging studies were performed to demonstrate equivalence of the CHX gel formulation in the present application to similar CHX solutions.

In the substantivity study the CHX gel or CHX solution formulation was applied to hydroxyapatite (HA) discs which were used as a substrate to demonstrate relative substantivity of gel vs solution. At the pH where the CHX gel was applied to the HA discs the overall net charge of HA would be negative, similar to skin, and as CHX is a positively charged ion it is expected that it would adhere to the negatively charged HA. The discs were subsequently rinsed in water to test the persistence of the topical application. These were applied to agar plates of a single bacterial species, S. aureus, and the zone of inhibition of growth measured. In this study the zone of inhibition of growth was comparable for both the CHX gel and CHX solution after rinsing for either 1, 4, 6 or 24 hours. Furthermore, it appeared that the time for which the disc was rinsed did not affect the efficacy of the CHX with the samples rinsed for 24 h appearing to have the largest zone of inhibition at 30 mm compared to a typical value of 25-26 mm for the 1, 4 or 6 hour rinsed discs. Although the study is limited by only being performed with duplicate samples and thus lacks statistical power it does suggest a trend towards supporting the proposed once daily dosing of the CHX gel.

In the second bridging study a kill-time test was performed to demonstrate equivalent between the CHX gel and CHX solution formulations in an *in vitro* antimicrobial efficacy test using three different indicator organisms, S. aureus, E. coli and K. pneumonia, which are known to be commonly found in umbilical cord infections. After contact periods of 30, 60 or 120 seconds both the CHX gel and CHX solution formulations demonstrated greater than 4 log10 reduction in bacterial numbers. The results of this *in vitro* kill-time study suggest that the antimicrobial activity and efficacy is equivalent between the CHX gel and CHX solution formulations. Although no discussion is provided as to the relationship between the concentration of both products used in the study and the pharmacodynamic response required for the proposed indication, it is accepted that the overall data and the extensive experience with the active drug substance suggest a likely clinical efficacy of the CHX gel in the proposed indication.

The bridging studies are offered to support the conclusion that the proposed CHX gel formulation is equivalent to the CHX solution formulation. Each of the *in vitro* kill time, substantivity and irritancy studies used the same 7.1% w/w chlorhexidine digluconate solution as the published clinical studies to bridge from the in vitro studies to the published clinical studies. The GSK CHX Gel was then compared with the 7.1% w/w chlorhexidine digluconate solution in the in vitro studies. Since the solution and the GSK CHX Gel were >99.99% effective in the in vitro kill time studies, and behaved similarly in the substantivity test, the solution and the CHX Gel are considered very likely to behave similarly when applied to neonates.

Based on the low systemic absorption of chlorhexidine from localised topical application no secondary pharmacodynamics effects are expected and safety pharmacology studies have not been performed for the current formulation in this application. This is accepted based on the extensive experience with the active

drug substance, its' low systemic absorbance upon topical application and the short duration of use. For similar reasons pharmacodynamic drug interactions have not been performed which is also acceptable.

2.3.3. Pharmacokinetics

No new nonclinical studies have been performed to assess the pharmacokinetics of the 7.1 % chlorhexidine digluconate gel as agreed in the previous scientific advice. Based on published studies it is evident that the absorption of topically applied CHX is limited to the upper layers of the skin with little evidence of systemic exposure. This poor absorption is most likely due to the cationic nature of the drug substance resulting in its strong binding to the skin.

Systemic absorption of chlorhexidine following umbilical cord cleansing has been assessed in two published PK studies which have demonstrated little to no absorption in full-term infants with some limited absorption in pre-term infants, most likely due to increased permeability of the epithelial barrier which may have been enhanced by the use of an ethanol based formulation. Very limited information is available as to the fate of systemically absorbed chlorhexidine, however, it is thought to undergo normal renal and hepatic metabolism with minimal metabolic cleavage.

4-chloroaniline (4-CA), a known degradation product of chlorhexidine was rapidly absorbed across the skin with a maximum systemic exposure within 3 hours with an AUC of 332.1 ng.hr/mL after application of 40 µL of 30% 4-CA to the dorsal skin or rats. A rapid absorption of this degradation compound with known toxicological effects is discussed further in the relevant toxicology section of this assessment (section 2.3.4). There is no metabolism induced formation of 4-CA.

2.3.4. Toxicology

A majority of the toxicology studies performed with chlorhexidine have been via oral administration either in drinking water or by gavage. The absorption via this route is thought to be limited and systemic exposure levels will be similar to that seen with topical application. The value of the acute and repeat dose toxicity studies is further limited by the fact that they are dated, not GLP compliant and have usual design studies making it difficult to determine NOELs. The ability to correlate effects is further hampered by the absence of fuller toxicokinetic parameters. However, it is acknowledged that these limitations are negated by the vast number of years clinical experience with topical chlorhexidine preparations.

Single dose toxicity

Single dose toxicity studies with chlorhexidine reveal an oral LD_{50} of between 2500 and 3000 mg/kg in rodents owing to the poor absorption by this route of administration. Using IV administration the LD_{50} in rodents was in the range of 21-25 mg/kg. No acute toxicity studies were reference for topical application of chlorhexidine, although, they are thought to be similar to those observed in the oral studies based on similarly poor absorption when administered by this means.

Repeat dose toxicity

Repeat dose toxicity studies have been performed in mice, rats and dogs for periods of up to 2 year with daily oral dosing. Findings of note include increases in the number of giant cells/histocytes in rodent, liver toxicity in dogs as well as respiratory symptoms upon auscultation. Limited toxicokinetic studies revealed low systemic chlorhexidine in the highest dose group, with levels generally undetectable in the other two treatment groups of 0.5 and 5 mg/kg/day. The majority of the chlorhexidine was found to accumulate in the liver and kidneys after 12 months of dosing.

Genotoxicity

Mutagenicity testing using the Ames test had equivocal results with technical difficulties due to the nature of the mechanism of action of chlorhexidine. A comet assay performed in mammalian CHO cells suggested that chlorhexidine was not genotoxic.

Carcinogenicity

Carcinogenicity studies at levels up to 400 mg/kg/day administered orally in mice for 18 months were negative. Similarly, in rats no evidence of carcinogenicity was noted in 2 year studies following administration of 50 mg/kg/day in the diet. When administered in the drinking water to rats at 40 mg/kg/day for 2 years no test article related neoplasms were found. In both the mouse and the rat studies measurable levels of the degradant, 4-chloroaniline, were present at levels up to 0.6 mg/kg/day without any adverse carcinogenicity findings.

Reproduction Toxicity

In reproductive toxicity studies no effects on either male or female fertility were seen with chlorhexidine administered orally in rats. Pregnancy rates were unaffected and only minor variations in mean pup weight and litter size were seen without reaching statistical significance. In studies of embryo-foetal development chlorhexidine was not teratogenic in rats and rabbits.

No juvenile toxicity studies have been performed and given the indicated patient population and duration of treatment this is considered acceptable.

Local Tolerance

Local tolerance of the proposed CHX gel formulation was tested in an *in vitro* skin irritancy test using the MatTek Effective Time-50 (ET-50) method developed for the validated EpiDerm EPI-200 Skin Model where cell viability is tested in normal human-derived epidermal keratocytes cultured to form a highly differentiated model of the human epidermis. In these studies, it is noted that the viability of the keratocytes is dramatically reduced by the CHX gel with viability at less than 10% within 5 hours of treatment. The ET-50

value (Effective Time where viability is reduced to 50%) for the CHX gel formulation is 1.99 hours and is in the range of the values for 1% SDS, which is classified as a moderate skin irritant with this system. When taken in the context that the 7.1% chlorhexidine digluconate solution used is identical to that used in the clinical studies where approximately 30,000 neonates have been treated with no adverse events consistent with cytotoxicity it is accepted that the gel is only a mild to moderate skin irritant.

Other toxicity studies

Studies on impurities:

4-chloroaniline (4-CA) is a known degradant of chlorhexidine digluconate and an impurity in all CHX products. 4-CA is a known carcinogen in rodent studies and on this basis is considered to be possibly carcinogenic in humans. The Applicant has proposed limits for 4-CA in the final drug product of 800 ppm on release and 4000 ppm at the end of shelf life which would equate to potential exposures to 170 µg or 852 µg of 4-CA respectively. The formation of 4-CA increases over time with hydrolysis of the chlorhexidine, increasing with increases in temperature. Based on the proposed levels of 4-CA at the end of life of the product the theoretical cancer risk is calculated to be less than 1 in 10^5 based on a maximum of 7 days usage and is in line with the principles of ICH M7 (R1) and deemed acceptable.

In addition to the carcinogenicity risk, 4-CA is also associated with increased levels of methaemoglobinaemia. 4-CA is rapidly and effectively absorbed through the skin. The proposed end of shelf life limits potentially suggest a sufficient margin of safety from the rodent studies performed, however, rodents can tolerate higher levels of 4-CA due to their ability to metabolise it quicker compared to humans. The currently proposed levels could potentially be associated with a risk of methaemoglobinaemia, particularly in pre-term infants. This topic is further discussed in the clinical part of this assessment report.

Phototoxicity:

Although raised as a potential issue during Scientific Advice, evidence is provided suggesting low potential risk of photo-allergic contact sensitisation and phototoxicity.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

2.3.6. Discussion on non-clinical aspects

As agreed in scientific advice obtained from the CHMP, no new non-clinical animal studies to demonstrate pharmacological action were performed for the indicated condition of umbilical cord infections and the Applicant relies on two *in vitro* bridging studies which were performed to assess substantivity and microbial activity of the proposed formulation. Each of the *in vitro* studies used the same CHX solution as the published clinical studies. The kill-time test was performed with three indicator organisms, *S. aureus*, *E. coli* and *K. pneumoniae*, which are known to be commonly found in umbilical cord infections, according to the published

data. The results showed that CHX gel containing 7.1% w/w and the chlorhexidine digluconate solution demonstrated a greater than 4 log10 reduction (> 99.99% kill) against the three indicator organisms. In addition, the substantivity study showed no difference in substantivity between chlorhexidine digluconate gel, 7.1% w/w (CHX Gel) and 7.1% w/w chlorhexidine digluconate solution. Therefore, the currently available clinical data in combination with the *in vitro* studies performed by the Applicant are sufficient to support the registration of this new chlorhexidine formulation for this indication.

The pharmacokinetics of chlorhexidine has been adequately addressed by literature review in the non-clinical package for this application. In addition the toxicological effects are considered to have been well characterised in the non-clinical package with both literature review as well as reference made to studies performed by the original innovator of chlorhexidine. To address local tolerance issues with the current proposed formulation the Applicant has performed *in vitro* skin irritation studies which have identified the CHX gel to be a mild to moderate skin irritant.

2.3.7. Conclusion on the non-clinical aspects

The applicant has submitted a non-clinical package sufficient to characterise the pharmacology, pharmacokinetics, and toxicology of Umbipro. From a non-clinical point of view there are no issues to preclude Umbipro being granted a positive scientific opinion.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The four clinical studies which provide principal evidence of efficacy and safety for chlorhexidine digluconate gel, 7.1% w/w (equivalent to 4% w/w chlorhexidine) (CHX Gel) are published studies and were not conducted by GSK [Mullany, 2006a, El-Arifeen, 2012, Soofi, 2012, Hodgins, 2012].

In an effort to confirm that these studies met the ethical requirements of Directive 2001/20/EC and were conducted in accordance with the Declaration of Helsinki that applied at the time the studies were conducted, GSK contacted the authors of the studies for information on the conduct of these four clinical trials.
For the Mullany study, the protocol was approved by Nepal Health Research Council and the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health. Oral consent was obtained, and the author has confirmed GCP compliance for the study.

For the El Arifeen study, the study protocol was approved by the ethics committee of the Johns Hopkins Bloomberg School of Public Health and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B).Oral consent was obtained and the author has confirmed GCP compliance for the study.

The Soofi study was approved by the Ethics Review Committee for Research at Aga Khan University (Karachi,Pakistan), written consent was obtained and the author has confirmed GCP compliance for the study.

The Hodgins study was approved by the Maternity Hospital Ethics Committee (non-inferiority study) and the Ethics Review Committee of the Nepal Health Research Council. The author has confirmed that written consent was obtained from mother or family member but no information is available regarding GCP compliance.

2.4.2. Pharmacokinetics

Chlorhexidine (CHX) Gel is intended to be administered topically to the cut umbilical cord stump once daily for up to the first seven days of life. Chlorhexidine is very poorly absorbed when administered topically in any species and this is due to its physicochemical properties as it is in the ionised form and has a molecular weight which is greater than the optimal weight for effective skin penetration.

Chlorhexidine permeates into and across adult skin poorly [Karpanen *et al*., 2008]. This study showed poor permeation of chlorhexidine through excised full-thickness human skin after 2 min and 30 min of exposure to aqueous 2% (wt/vol) CHG. The levels of CHG were highest within the top 10 µm sections of skin and remained consistently low within the deeper layers.

Also, poor topical absorption of chlorhexidine was illustrated in a study where radiolabelled chlorhexidine formulated as a 4% hand wash or 5% aqueous solution was applied to adult forearm skin and left in contact for 3 hours. Levels ranging from 81- 98% of the radioactivity were subsequently recovered from the skin. No radioactivity was detected in blood or urine [Case, 1976].

Specific pharmacokinetic studies investigating the systemic absorption of chlorhexidine following umbilical cord cleansing are limited to two published studies [Aggett, 1981 and Johnsson, 1987].

In the Aggett study, full and preterm infants received daily umbilical cord cleansing with 1% chlorhexidine in ethanol. After 9 days, median plasma levels of chlorhexidine were higher in preterm (n=23, 32 ng/mL) than full-term infants (n=25, 0 ng/mL). A subsequent group of 29 preterm infants received umbilical application of 1.0% chlorhexidine in a non-ethanol formulation. Of the 4 (14%) infants with detectable chlorhexidine levels, 3 had had umbilical cord catheters treated with the ethanol-based formulation. It was suggested by the study authors that the addition of ethanol (known to increase skin permeability), may have further increased the preterm infants' skin permeability.

In the Johnsson study from 1987, in 44 infants (21 vaginal delivery, 23 caesarean section) who received 5 consecutive days of cord cleansing with 4% chlorhexidine gluconate solution, day 5 serum samples were negative in all but 1 infant. Contamination from the infant's skin surface when performing venepuncture could not be ruled out because this infant was vaginally delivered and mothers underwent chlorhexidine cleansing of the perineum and vulva before delivery.

Further published data are available regarding the systemic absorption of chlorhexidine following topical application for body washing in neonates. Of six studies that evaluated chlorhexidine absorption after skin cleansing or full body bathing, four studies showed some absorption of chlorhexidine in some infants, with two of these enrolling preterm infants.

The umbilical cord is covered by a simple epithelium of amniotic derivation, which becomes stratified in late gestation. The epidermal barrier develops from about 23 weeks gestation, maturing around 32 weeks

[Rutter, 2003]; the cutaneous permeability of the human newborn decreases with gestational age [Nachman, 1971].

Therefore, there is a possibility that chlorhexidine applied to the cord stump could be more readily absorbed in preterm infants than term infants. However, even if this did occur, it would likely be in such small amounts to be of no clinical significance. The available published data do not suggest that there would be any safety concerns if systemic absorption did occur.

2.4.3. Pharmacodynamics

Mechanism of action

The drug substance, chlorhexidine digluconate, a cationic bis-biguanide molecule, is an effective broad spectrum topical antibacterial substance with a high initial bactericidal effect and a prolonged bacteriostatic action. It is bactericidal or bacteriostatic against a wide range of Gram-negative and Gram-positive bacteria and is also active against yeasts, fungi, some protozoa and some viruses (including HIV) [Denton, 2001; Martindale, 2014; Harrison, 1998]. The effects of chlorhexidine which is cationic result from its ability to bind to negatively charged surfaces to cause either a bacteriostatic or bactericidal effect [Martindale, 2014].

The mechanism of action arises from electrostatic attraction between the positively charged chlorhexidine and the negatively charged bacterial cell wall. The interaction causes inhibition of membrane enzymes and disruption of the cell membrane leading to leakage of cellular components. These mechanisms may sub-lethally injure microbial cells, or cause cell death, depending on the severity of the membrane damage. Penetration of the chlorhexidine molecule into the cytoplasm of the cell, results in precipitation of cytoplasmic constituents and cell death [Hugo, 1964].

2.4.4. Discussion on clinical pharmacology

Umbipro is administered to newborn children and administration is local. Chlorhexidine does not appear to be significantly absorbed through intact skin in the newborn although there is some evidence that absorption could be increased in premature infants.

2.4.5. Conclusions on clinical pharmacology

Umbipro is intended only for local administration to new born children. Chlorhexidine does not appear to be significantly absorbed through intact skin in the newborn although there is some evidence that absorption would be increased in premature infants, and the SmPC should reflect the potential risk associated with use in such babies.

The mechanism of action for this locally applied locally active compound has been adequately characterised.

2.5. Clinical efficacy

2.5.1. Main studies

Summary of main efficacy results

Mullany L, Darmstadt G, Khatry S, *et al*. Topical applications of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomised trial. *Lancet* 2006(a); 367: 910-8.

El-Arifeen S, Mullany L, Rasheduzzaman S, *et al*. The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster randomised trial. *Lancet* 2012; 379: 1022-8.

Soofi S, Cousens S, Imdad A, *et al*. Topical applications of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan: a community-based, cluster-randomised trial. *Lancet* 2012; 379: 1029-36.

Hodgins S, Thapa K, Khanal L, *et al*. Chlorhexidine gel versus aqueous for preventive use on umbilical stump: a randomized noninferiority trial. *Pediatr Infect Dis J* 2010; 29(11): 999-1003.

The dossier to support clinical efficacy and safety is primarily literature-based. Principal evidence of efficacy has been derived from:

1) three large published community-setting randomised controlled trials which evaluated the use of chlorhexidine digluconate 7.1% liquid prepared by diluting a 20% chlorhexidine digluconate solution (4% chlorhexidine)

   and

2) a published non-inferiority randomised study comparing the performance of a chlorhexidine digluconate 7.1% (4% chlorhexidine) gel with a chlorhexidine digluconate 7.1% (4% chlorhexidine) solution.

In vitro antibacterial equivalence and skin-irritancy studies have been conducted to bridge efficacy and safety data from the published studies of chlorhexidine digluconate 7.1% (4% chlorhexidine) solution to the GSK CHX Gel. Further evidence of the safety of chlorhexidine has been derived from the literature.

These data were reported by the UN Commission on Commodities for Women's and Children's Health as being sufficient to support the inclusion of chlorhexidine gel in the list of Essential Medicines for Children, along with their recommendation for its topical use in the first week of life for the prevention of umbilical cord infections, as previously reported in 2012 by Segre *et al*. In addition, the three interventional country-based studies formed the basis of a Cochrane Collaboration review, which also recommended the use of chlorhexidine for the prevention of umbilical cord infections in neonates in the community and primary care settings only (Imdad *et al*, 2013).

No additional specific clinical or safety studies on the proposed chlorhexidine gel have been conducted. Scientific Advice was sought from the European Medicines Agency in 2013 and this approach was agreed in principle.

A brief description of the published community-setting randomised controlled trials is provided below:

Nepal [Mullany, 2006]

This was a community-based, double-masked, cluster randomised trial of 15,123 infants. The cord cleansing trial was nested within a study of the effect of full-body cleansing with antiseptic on neonatal mortality. The study was approved by the Nepal Health Research Council and the Committee on Human Research of the Johns Hopkins Bloomberg School of Public Health. Study procedures were explained to pregnant women 6 months into pregnancy, and oral informed consent obtained. In each of the two skin cleansing groups, clusters were randomised to one of three cord-care regimens: 7.1% chlorhexidine digluconate (prepared by diluting 20% chlorhexidine digluconate to the appropriate concentration with purified water), soap and water or dry cord care. Community-health workers were blinded to chlorhexidine and the soap water but not to dry cord care. Cleansing was administered on days 1-4, 6, 8 and 10. After handwashing with soap and water, the care worker moistened a cotton ball with solution and gently dabbed the umbilical cord stump. A second soaked ball was used to cleanse the base of the stump and the skin around the base. The primary outcomes were incidence of neonatal omphalitis and neonatal mortality. The study was designed to detect a minimum 25% relative reduction in incidence of cord infection, given 80% power and 5% two-sided type 1 error. The expected omphalitis rate in the dry cord care group was 10.5 per 100 live births. Neonatal mortality was expressed as deaths per 1000 live births. Omphalitis was defined under three categories of severity: moderate redness extending to the abdominal skin at the base of the cord stump; redness as above with pus or severe redness extending further than 2 cm from the base with or without pus; severe redness, extending further than 2 cm from the base, with pus. A total of 15,123 newborn infants were enrolled with 4,934 infants in the chlorhexidine clusters, 5,107 in the soap and water and 5,082 in the dry cord care clusters. In the chlorhexidine group, severe omphalitis was reduced by 75% (RR 0.25, 95% CI 0.12- 0.53). Soap and water cleansing did not reduce infection rates over dry cord care. Neonatal mortality was 24% lower in the chlorhexidine group (RR 0.76, 95% CI 0.55- 1.04) than in the dry cord care group. In infants enrolled within the first 24 hours of life, mortality was significantly reduced by 34% in the chlorhexidine group (RR 0.66, 95% CI 0.46- 0.95). Time to first cleansing had an impact on efficacy– there was stronger evidence of protection against infection in infants enrolled within 24 hours of birth for all three grades.

Bangladesh [El-Arifeen, 2012]

This was a community-based, cluster randomised trial which enrolled 29,760 newborn infants. The study protocol was approved by the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh. Twenty-two unions in three sub-districts (an estimated total population of 546,000 people) participated in the study; the area was divided into 133 clusters on the basis of population size (mean size 4,100, range 2,071- 5,598). In each cluster, a female community health worker provided a basic package of newborn care interventions, including messages to keep the cord clean and to avoid the application of potentially harmful substances. The clusters were randomly allocated to one of three regimens: 1) multiple chlorhexidine cleansing group - cleansing as soon as possible after birth and once daily for 7 days, 2) single

chlorhexidine cleansing group – cleansing as soon as possible after birth and 3) dry cord care group – no specific umbilical cord care beyond basic messages relating to clean cord cutting and avoidance of home-based applications to the cord. Community-health workers were not masked to the treatments. Verbal consent was obtained from the pregnant women. The 4% chlorhexidine solution was prepared by diluting a 20% stock solution of aqueous chlorhexidine digluconate with distilled water. The primary outcome for this study was death within 28 days after birth per 1000 live births. The umbilical cord stump was examined for redness, pus and swelling. Pus was defined as present or absent, whilst redness and swelling were categorised into four severities: none, mild (restricted to the stump) moderate or severe (moderate and severe classifications required extension to the skin around the base of the stump <2 cm or ≥2 cm, respectively). Omphalitis was defined for analysis under various sign-based algorithms representing mild, moderate or severe. A data safety monitoring board reviewed results of two interim analyses with 31.3% and then 69.8% of the data, and recommended continuation of the study as planned. This study showed that the risk of neonatal mortality was reduced by 20% in the single day cleansing group compared with the dry cord care group: 22.5/1000 births versus 28.3/1000 (RR 0.80, 95% CI 0.65- 0.98). There was no statistically significant difference for the relative risk of neonatal mortality between the multiple cleansing and the dry cord care group (RR 0.94, 95% CI 0.78- 1.14). The risk of severe cord infection was reduced by 65% in the multiple cleansing group compared with dry cord care: 4.2/1000 versus 12.4/1000 live births (RR 0.35, 95% CI 0.15- 0.81), respectively. A statistically significant reduction on severe cord infection was not observed in the single cleansing group (RR 0.77, 95% CI 0.40- 1.48).

The findings of this study that multiple cleansing with chlorhexidine did not reduce neonatal mortality contrasts with the results of the Nepal study by Mullany et al. The authors discussed possible reasons for the absence of mortality effect in the multiple cleansing group, including the possibility that the study group was different in some way resulting in an increased underlying risk (although the three groups were balanced), poorer delivery of the intervention in the multiple cleansing group (no difference between the three groups in the timing of initiation of the interventions) or that this was a chance finding (a "type 2 error" i.e. missing a true effect due to lower than expected study power). The mortality effect in all enrolled babies was greater in babies with a low birthweight (<2500 g) and preterm (<37 weeks) babies but when analysis was done with data from individual groups the effect was only statistically significant in preterm infants in the single-cleansing group (35%, 95% CI 14- 50; p=0·002).

Pakistan [Soofi, 2012]

This was a two by two factorial, cluster randomised trial of 9,741 newborn infants. The study was approved by the Ethics Review Committee for Research of the Aga Khan University, Karachi, and overseen by an independent data safety and monitoring board, which ratified the design, met twice to assess data, and recommended completion of the study as per protocol in its final meeting. Clusters were typically one or two villages served by a traditional birthing attendant. One hundred and eighty seven (187) clusters (comprising 11,886 live births of which 9,741 were eligible) were randomised to one of four regimens, chlorhexidine and hand-washing, hand-washing only, chlorhexidine only, standard dry cord care. The community-health care workers who collected the outcome data were masked to the treatments. A 4% free chlorhexidine solution was prepared by diluting 20% chlorhexidine digluconate in distilled water. The consenting procedure was not reported but personal communication with the author indicated that written consent was obtained (May 2015). Caregivers were advised to apply the chlorhexidine once a day for 14 days after birth regardless of the status of the umbilical cord. A cotton ball moistened with chlorhexidine solution was dabbed onto the stump of the cord and a second moistened ball was used to cleanse the base of the stump and the skin

around the base. The primary outcomes of the trial were neonatal omphalitis and neonatal mortality. Omphalitis was categorised into four degrees of severity: no omphalitis, mild omphalitis (redness, swelling, or pus restricted to the cord stump), moderate omphalitis (redness, swelling or pus extending to the skin at the base of the cord stump less than 2cm) or severe omphalitis (inflammation extending more than 2cm from the cord stump, with or without pus). There was a 42% reduction in omphalitis in the chlorhexidine groups compared to no chlorhexidine (RR 0.58, 95% CI 0.41- 0.62). There was statistical evidence of a reduction in neonatal mortality in those who received chlorhexidine cleansing (RR 0.62, 95% CI 0.45- 0.85) but no evidence of an effect of handwashing promotion on reduction in neonatal mortality (RR 1.08, 95% CI 0.79- 1.48).

A summary of study design /efficacy results for the main trials submitted in support of the application is provided below.

Table 2 Summary of study design of published randomised controlled trials and non-inferiority study of 7.1% Chlorhexidine digluconate

Study	Mullany, 2006a	El-Arifeen, 2012	Soofi, 2012	Hodgins, 2010
Design	Cluster randomised controlled trial	Cluster randomised controlled trial	2x2 factorial design cluster randomised controlled trial	Non-inferiority individually randomised
Country	Nepal	Bangladesh	Pakistan	Nepal
Duration of trial	Nov 2002 – Mar 2005	Jun 2007 – Sep 2009	Jan 2008 – Jun 2009	Jan 2009 – May 2009
% home births [Imdad, 2013b]	92%	93%	80%	N/A
Inclusion criteria	All live births in study area	All live births in study area	All live births in study area attended by participating traditional birth attendant	Normal vaginal deliveries in maternity hospital
Key exclusion criteria	Not treated within 10 days after birth	Not treated within 7 days after birth	Not treated within 3 days after birth; Babies with congenital anomalies	Birth weight <2000g; Complicated delivery; Clinically evident umbilical infection
Primary outcomes	Neonatal mortality; Omphalitis	Neonatal mortality; Omphalitis[1]	Neonatal mortality; Omphalitis	Bacterial growth 24 hours after chlorhexidine application
Chlorhexidine Formulation	4% Solution	4% Solution	4% Solution	4% Gel; 4% Aqueous solution
Chlorhexidine groups (Frequency)	Multiple (seven applications on days 1-4, 6, 8, 10)	Multiple (daily for 7 days); Single application in first 24 hours)	Multiple (daily for 14 days); Multiple with hand-washing	Gel (application in first 3 hours); Solution (application in first 3 hours)
Comparison groups	Soap/water; Dry cord care	Dry cord care	Hand-washing; Dry cord care	N/A
Total sample size (Treated with Chlorhexidine)	15,123 (4,934)	29,760 (19,752)	9,741 (4,867)	694 (694)
Observed mortality risk per 1000 live births, control arm(s)	19.2	28.3	36.1	N/A
Relative risk (RR) (95% confidence interval, CI) neonatal mortality chlorhexidine vs control	Chlorhexidine vs dry cord care: 0.76 (0.55- 1.04) Enrolled <24hrs after birth [N=9,457] Chlorhexidine vs dry cord care: 0.66 (0.46- 0.95)	Multiple Chlorhexidine vs dry cord care: 0.94 (0.78-1.14) Single Chlorhexidine vs dry cord care: 0.80 (0.65- 0.98)	Chlorhexidine (with/without hand-washing) vs no chlorhexidine (dry cord care or hand washing): 0.62 (0.45-0.85)	N/A (Non-inferiority of gel to solution demonstrated)

[1] Outcome but not specifically stated as primary

According to the UN Commission report, all three studies showed substantial reductions in neonatal mortality (20% to 38%) and even greater reductions in omphalitis (24% to 75%) in the chlorhexidine groups, with greater efficacy being reported with early application (within 24 hours of birth). This assessment is endorsed.

The three community-based studies were included in a pooled analysis in a Cochrane systematic review, "Umbilical cord antiseptics for preventing sepsis and death among newborns", published in 2013. This

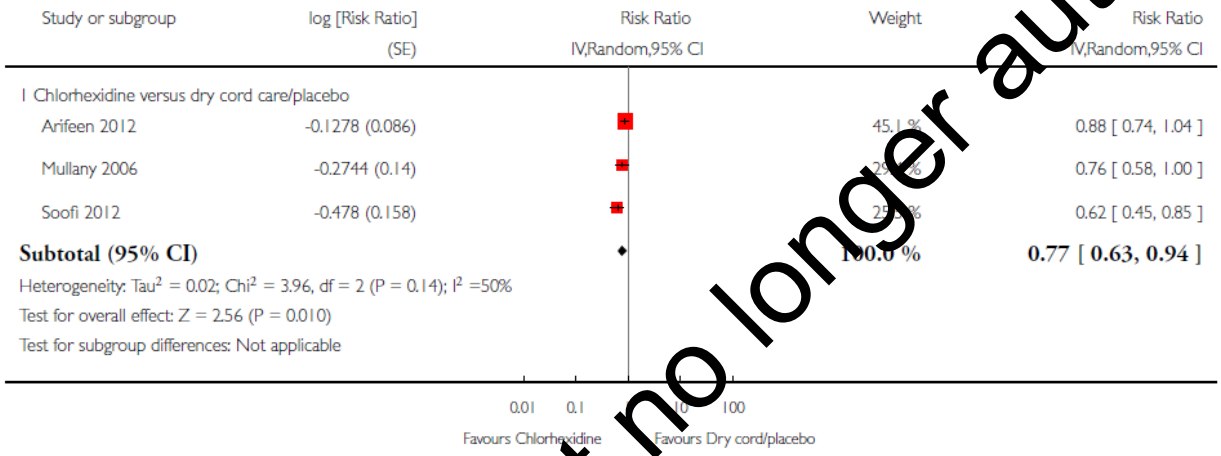
systematic review also included 31 studies conducted in hospital settings mostly in developed countries. That analysis supported the use of chlorhexidine in community and primary care settings in developing countries, but not so in hospital settings in developed countries. These data were further reviewed in 2015, with a similar recommendation being produced.

Analysis 1.1. Comparison 1 Antispetics vs dry cord care/placebo. Studies conducted in community settings, Outcome 1 All-cause mortality.

Review: Umbilical cord antiseptics for preventing sepsis and death among newborns

Comparison: 1 Antispetics vs dry cord care/placebo. Studies conducted in community settings

Outcome: 1 All-cause mortality



There is less evidence of a beneficial effect with the use of chlorhexidine in hospital settings, although many of the studies analysed in the various systematic reviews were conducted in developed rather than developing countries, and so the populations and healthcare practices might have been different. As such, the use of chlorhexidine is not recommended in hospital settings, except as a substitute for the use of traditional cord preparations such as cow dung, which are commonly used in some communities.

Other studies have investigated lower chlorhexidine concentrations than that investigated in the three studies summarised above, but the numbers enrolled in those studies are substantially lower than the country-based studies, and as such it is not possible to draw meaningful conclusions from those studies, either regarding the efficacy of those lower concentrations in themselves or in comparison with the 4% equivalent concentration used above, for the prevention of umbilical cord infections in the community and primary care settings in developing countries.

Bridging of published efficacy data to gel formulation

The studies described above used chlorhexidine aqueous solution, rather than the currently proposed gel formulation. In order to determine whether these data can be used to establish the efficacy of a gel formulation containing an equivalent concentration of chlorhexidine, a randomised, non-inferiority study was conducted to determine whether there was a difference in peri-umbilical colonisation 24 hours post

application of the text and reference formulations (Hodgins *et al*, 2010). 4% chlorhexidine aqueous solution was compared with 4% gel.

The non-inferiority margin was 10% and it was estimated that 295 babies per group would be required to establish non-inferiority of gel with aqueous preparations, with 80% power and 5% type I error rate. At baseline, the proportion of infants with positive swabs was 33.9% in the gel group and 29.4% in the aqueous group. At 24 hours post application, the proportion positive was reduced in both groups: 4.6% in the gel group and 10.7% in the aqueous group. The absolute difference in proportion positive (gel minus aqueous) was -6.1% (95% CI: -10.2% to -2.1%). There were no significant differences between the groups with regards to bacterial species at baseline.

An additional *in-vitro* kill-time test which evaluates in-vitro antimicrobial efficacy by examining the rate at which concentrations of an antimicrobial agent kill a bacterial isolate has also been conducted. Chlorhexidine digluconate gel, 7.1% w/w and chlorhexidine digluconate solution, 7.1% w/w were compared using Staphylococcus aureus, Escherichia coli and Klebsiella pneumonia as indicator organisms and the results showed that both formulations had significant antimicrobial activity and demonstrated equivalent kill in a suspension test after a 2 minute contact time.

Overall, the clinical and *in-vitro* data support the bridging of the clinical efficacy results to the applicant's product.

2.5.2. Discussion on clinical efficacy

Initiation and duration of treatment

Results from the Mullany study support the early application (within 24 hours of birth) of chlorhexidine to the cord stump. The evidence to support either single or multiple applications as being superior is less conclusive. The Cochrane systematic review conducted in 2013 demonstrated a statistically significant improvement in the clearance of *Staphylococcus Aureus* and *E.coli* (but not Streptococcal) colonisation with multiple once-daily applications than a single application of chlorhexidine. There was also a statistically significant reduction in the incidence of moderate and severe omphalitis with multiple applications than with a single application, but no difference in overall mortality between the two groups.

The current WHO guidelines on the duration of use of chlorhexidine in this setting recommend once daily application for 7 days which is endorsed. This being said, the WHO acknowledge that individual countries may recommend a single application only, in line with their local guidelines. This has been reflected in the product information.

Use in Preterm infants

The data regarding the use of chlorhexidine in preterm infants (gestational age < 37 weeks) are limited. A sub-analysis of this population was performed in the study by El-Arifeen *et al*, and while the data did show a trend towards an improvement in mortality, a statistically significant result was only obtained in preterm infants receiving a single administration of chlorhexidine. It is probable that the number of subjects in this population was not sufficient to appropriately power an analysis of the effect of multiple applications versus single application. This being said, it is reasonable to presume that the risk of microbiological contamination would be similar in preterm infants as term infants when delivery occurs in similar settings.

The dermis in preterm infants is not fully developed until after 32 weeks of gestation, and as such there is the theoretical possibility of an increased risk of absorption of chlorhexidine and its degradation products in infants below this gestation age. However, the limited data generated in this population in the previously referenced studies do not suggest an increased risk associated with the use of the product in this population, but do suggest a significant benefit in reducing the risk of omphalitis and associated complications in preterm neonates. As such, it is neither reasonable nor appropriate to restrict the use of 7.1% chlorhexidine gel to infants above this gestational age, and therefore no such restriction will be added to the product information.

Additional expert consultation

None

2.5.3. Conclusions on the clinical efficacy

Overall, the literature data presented, along with the systematic review results which are in the public domain, support the use of chlorhexidine gel for the prevention of umbilical cord stump infections in the immediate postnatal period, when such deliveries have occurred in community or primary care settings in developing countries. The evidence also supports the early (within 24 hours) initiation of treatment, and the continuation of daily cleansing for 7 days post-delivery. There is little evidence to support the use of chlorhexidine in this indication in hospital settings in developed countries.

While the evidence regarding the use of chlorhexidine in premature infants is less robust, there would appear to be no basis for the restriction of the use of the product in this population.

2.6. Clinical safety

Chlorhexidine has a well-characterised safety profile from over 60 years post-marketing experience and has been licensed for use in a variety of ways including as hand washes, preoperative body showering and skin disinfection, wound care and oral hygiene. Common formulations of chlorhexidine include aqueous and alcohol-based solutions, gels, and powders; all have been used topically on adult, infant and neonatal skin. The level of clinical exposure to chlorhexidine over this period helps to provide a very clear indication of the likely risks associated with using chlorhexidine in different patient groups.

The clinical safety data in support of this application consist of three large published community-setting randomised controlled trials in resource-poor settings which evaluated the use of 7.1% chlorhexidine digluconate liquid prepared by diluting a 20% chlorhexidine digluconate solution (4% chlorhexidine) [Mullany, 2006a; El-Arifeen, 2012; Soofi, 2012] and a published non-inferiority, randomised study comparing the performance of a 7.1% chlorhexidine digluconate (4% chlorhexidine) gel with 7.1% (4% chlorhexidine) solution [Hodgins, 2010].

Patient exposure

As well as extensive data on experience with chlorhexidine products used in various cleansing interventions, the specific safety of CHX Gel for the prevention of omphalitis is supported in this application by published

clinical data from more than 30,000 neonates who have received chlorhexidine-based umbilical cord cleansing.

Adverse events

Due to its cationic properties, chlorhexidine binds strongly to skin, mucosa, and tissues, (being very poorly absorbed). In keeping with this, the most commonly reported events from post-marketing data and clinical trials of all GSK's chlorhexidine gluconate oral care products, (which provides supportive evidence of the safety profile of chlorhexidine) are: coated tongue, dry mouth, aguesia/dysguesia, oral paraesthesia /hypoaesthesia and glossodynia. In addition, there have been isolated post-marketing reports of hypersensitivity/anaphylaxis, reversible discolouration of teeth and tongue, irritation of the mouth, desquamation/swelling of oral mucosa and parotid gland swelling.

Known safety issues relating to the topical use of chlorhexidine products include skin irritation and systemic hypersensitivity reactions/ anaphylaxis. Other potential safety considerations relate to a risk of chemical burns in premature infants, systemic absorption and the presence of a trace impurity present in all chlorhexidine products: 4-chloroaniline (4-CA), which is associated with methaemoglobinaemia and a theoretical increased cancer risk.

Skin irritation and Hypersensitivity

Although uncommon (≥1/1000 and <1/100), the most commonly reported adverse events for topically applied chlorhexidine are contact dermatitis and photosensitisation [Chapman, 2012].

Due to a less developed stratum corneum, there is a theoretical risk that skin irritation and hypersensitivity could be worsened in premature infants. In the Bangladesh study, 21% of infants were born preterm, less than 37 weeks gestation [El-Arifeen, 2012]. The applicant has contacted the authors of the Nepal and Pakistan studies who indicated that approximately 15% in the Nepal trial and 20- 30% in the Pakistan trial were preterm (personal communication, 2014 and 2015). In 2010 in Pakistan, the preterm birth rate (less than 37 weeks gestation) was 15.2% and in Bangladesh, 14.0% [Blencowe, 2012]. No specific adverse events were recorded in the three published studies. Literature references describe chemical burns in preterm infants where certain alcohol based chlorhexidine topical disinfectants (concentrations ranging from 0.5- 2%) were applied [Mannan, 2007; Upadhyayula, 2007]. However, in all cases the authors attribute these reactions to the alcohol content of the formulations used rather than the chlorhexidine.

With specific regard to the topical application of chlorhexidine to newborn skin, transient contact dermatitis was reported in preterm (< 28 weeks gestation) very low-birth-weight infants after long-term (> 7 days) placement of chlorhexidine-impregnated dressings for central venous catheters. The effect may have been caused by the occlusive placement of the dressing rather than the chlorhexidine itself [Mullaneyb, 2006].

Contact dermatitis has not been reported in infants receiving full-body wiping, bathing, or umbilical cord cleansing with chlorhexidine. Transient bradycardia was reported in a breast-fed infant whose mother's breast was sprayed with chlorhexidine [Quinn, 1989].

GSK has conducted an *in-vitro* skin irritancy study comparing chlorhexidine digluconate 7.1% solution with CHX Gel which showed that the irritancy potential of gel and solution were no different; both were moderate irritants.

The CHMP comments that the proposed CHX gel formulation does not contain alcohol and occlusive dressings are not recommended. The incidence of contact dermatitis with use of the CHX gel formulation for newborn umbilical cord cleansing is therefore expected to be low.

Systemic hypersensitivity / anaphylaxis

There have been isolated reports of anaphylaxis in a wide variety of medicinal products and devices containing chlorhexidine. In 2012, the Medicines and Healthcare products Regulatory Agency, UK (MHRA) issued a medical device alert relating to the risk of anaphylactic reaction due to chlorhexidine allergy and recommending that medical and nursing staff members are made aware of the potential for this to occur [MHRA, 2012].

The frequency following use of CHX Gel is unknown but is expected to be very rare because no anaphylaxis cases were reported in the four large published randomised controlled trials involving 20,247 newborns exposed to chlorhexidine digluconate 7.1% solution.

CHMP concludes that the frequency of systemic hypersensitivity/anaphylaxis is expected to be very rare. The proposed Summary of Product Characteristics (SmPC) and Package Leaflet (PL) provide advice on the recognition of symptoms and signs of anaphylaxis as well advice to discontinue treatment and seek medical advice if this occurs.

Chemical Burns

In its Drug Safety Update in June 2014, the MHRA highlighted the risk of chemical burn injury to skin in premature infants following use of chlorhexidine solutions [MHRA, 2014]. It had received 14 reports of serious side effects in premature infants following treatment with chlorhexidine solution prior to central venous catheterization. Most cases happened when pooling occurred around the umbilicus or under the infant, in infants less than 32 weeks gestation and within the first few days of life when alcohol-based solutions or 2% aqueous solutions were used. This issue was reviewed at a European level by the Pharmacovigilance Risk Assessment Committee (PRAC) in September 2014. It recommended that Section 4.4 and Section 4.8 of the SPCs of chlorhexidine cutaneous solutions are amended to warn healthcare providers that chlorhexidine solutions used for skin antisepsis prior to invasive procedures have been associated with chemical burns in neonates (especially those born before 32 weeks of gestation and within the first 2 weeks of life) [PRAC, 2014].

CHMP comments that the applicant acknowledges that there is a risk of skin reactions and chemical burns with use of chlorhexidine topical disinfectants in pre-term infants, more so in extremely pre-term infants. The applicant has presented evidence from clinical trials and from case reports that these risks are exposure related and can therefore be mitigated by limiting exposure. This product does not contain alcohol and a single dose of CHX Gel for preterm infants born at <32 weeks gestation or weighing < 1500g is proposed. It is therefore considered acceptable not to exclude preterm infants born at <32 weeks gestation. The applicant has performed tests for pooling with the proposed amount of this gel formulation showing that pooling does not occur.

Delay in time to cord separation

Measures to keep the umbilical cord clean may delay the time to cord separation [Mullaney, 2006c]. Some delay in time to cord separation was reported in two of the three published community-based randomised

studies. In the Nepal study, among infants who received chlorhexidine cleansing, the mean time to separation was 5.32 +/- 2.4 days, whereas the mean ages at cord separation for infants in the soap/water and dry cord care groups were 4.25 +/- 1.6 days and 4.24 +/- 1.6 days, respectively [Mullaney, 2006c]. In rural Bangladesh, the mean age at cord separation for babies receiving single (6.90 days) or multiple (7.49 days) cleansings of the cord with chlorhexidine was increased by 2.1 and 2.69 days, respectively, compared to the dry cord care group (4.78 days) [Mullaney, 2013]. In the Pakistan study there was no difference in cord separation time between infants receiving different cord care regimens [Soofi, 2012]. In Nepal and Bangladesh, separation time was also examined for association with increased infection; no association was found.

CHMP concludes that although there is some evidence that measures to keep the umbilical cord clean may delay the time to cord separation, no association with increased infection is reported and therefore not felt to be clinically significant.

Systemic absorption

Due to its cationic properties, chlorhexidine binds strongly to skin, mucosa, and tissues, (being very poorly absorbed). Chlorhexidine is poorly absorbed through the skin.

The umbilical cord is covered by a simple epithelium of amniotic derivation, which becomes stratified in late gestation. The epidermal barrier develops from about 23 weeks gestation, maturing around 32 weeks [Rutter, 2003]; the cutaneous permeability of the human newborn decreases with gestational age [Nachman, 1971].

CHMP concludes that there is a possibility that chlorhexidine applied to the cord stump could be more readily absorbed in preterm infants than term infants. However, even if this did occur, it would likely be in such small amounts as to be of no clinical significance. The available published data do not suggest that there would be any safety concerns if systemic absorption did occur.

4-Chloraniline and Methaemoglobinaemia

The aromatic amine para-chloraniline also known as 4-chloroaniline (4-CA) is a starting material used in the production of chlorhexidine and it is a trace impurity in chlorhexidine products. From the available limited data, it is not possible to definitively quantify the minimum exposure of 4-CA leading to methaemoglobinaemia in human neonates or to define an acceptable upper threshold for 4-CA. However, the risk of methaemoglobinaemia following localised and short-term administration of chlorhexidine digluconate gel is considered to be sufficiently low that any occurrences will be very rare.

Of the approximately 30,000 babies treated with topical 7.1% chlorhexidine digluconate in the published efficacy studies described above, no cases of methaemoglobinaemia were reported, although the low-resource context of the studies would have made detection challenging. No serious adverse effects, including methaemoglobinaemia were reported in two published studies which evaluated the use of a cloth impregnated with 2% chlorhexidine gluconate for daily whole body bathing in a US intensive care setting, one of which was in paediatric patients and included 4,947 admissions [Climo, 2013; Milstone, 2013].

CHMP comments that the proposed product is for topical application and for short-term use (≤7days). The potential risk of methaemoglobinaemia is expected to be very rare. The applicant has provided further reassurance that the risk of methaemoglobinaemia following localised and short-term administration of CHX

Gel, although uncertain, is considered to be low throughout the product shelf-life. The SmPC and PL have been updated with appropriate cautionary warnings.

4-Chloraniline and Genotoxic risk

4-CA is genotoxic in mammalian cells [Mitchell, 1988; Anderson, 1990], mutagenic in the Ames assay [Mortelmans, 1986] and carcinogenic in the male rat and mouse [NIH Publication No. 89-2806]. These 4-CA carcinogenicity studies have been reviewed and included in the Carcinogenic Potency Database (CPDB) [Carcinogenicity Potency Database, 2011]. There are no data to show that 4-CA is carcinogenic in humans, however the International Agency for Research on Cancer (IARC) considers 4-CA to be possibly carcinogenic in humans based on animal data.

Six month stability data have shown that the 4-CA level at 30^0 C/35% relative humidity is a maximum of 800 ppm with respect to chlorhexidine digluconate. Based on projections from stability data to date, the 4-CA level will not exceed 4000 ppm with respect to chlorhexidine digluconate throughout the proposed 24 month shelf-life. The theoretical additional lifetime risk of cancer at this level, 5 in 10^6, is minimal and falls within the 1 in 10^5 risk of cancer (equivalent to 7800 ppm) stated in ICH M7.

GSK has taken all reasonable measures to minimise the 4-CA level in the drug product.

These include sourcing quality drug substance from a reputable supplier, controlling the level of this impurity in the input drug substance and applying appropriate controls during the manufacturing process

CHMP concludes that the theoretical lifetime cancer risk is minimal (approximately 5 per million).

Serious adverse event / deaths / other significant events

Approximately 30,000 neonates have received a range of chlorhexidine-based cleansing interventions including full-body cleansing and umbilical cord cleansing, without significant reported adverse effects. Although adverse event rates were not included in the published efficacy studies for umbilical cord care, in these studies, death was a primary efficacy endpoint and acute all-cause neonatal mortality was significantly reduced in the chlorhexidine treated infants compared to dry-cord care and/or soap and water. This indicates that any potential mortality risk associated with adverse effects of chlorhexidine application is still considerably outweighed by the benefit of reduced incidence of umbilical cord infection.

Laboratory findings

Not applicable.

Safety in special populations

The specific safety of CHX Gel for the prevention of omphalitis is supported by published clinical data from more than 30,000 neonates who have received chlorhexidine-based umbilical cord cleansing. The studies were performed in the population relevant to the proposed indication. No significant safety issues are reported. Further data was requested on use in infants <32 weeks gestation and low birth weight. The applicant presented evidence from clinical trials and from case reports that these risks are exposure related

and can therefore be mitigated by limiting exposure. This product does not contain alcohol and a single dose of CHX Gel for preterm infants born at <32 weeks gestation or weighing < 1500g is proposed. It is therefore considered acceptable not to exclude preterm infants born at <32 weeks gestation.

Immunological events

The frequency of systemic hypersensitivity/anaphylaxis is expected to be very rare. The proposed Summary of Product Characteristics (SmPC) and Package Leaflet (PL) include advice to discontinue treatment and seek medical advice as well as recognition of symptoms and signs of anaphylaxis.

Safety related to drug-drug interactions and other interactions

Chlorhexidine is not known to interact with any other drug substances, but is known to be incompatible with anionic agents [Martindale, 2014]. These incompatibilities could include soaps, alginates and sodium lauryl sulphate.

Only local interactions would be relevant and the chlorhexidine is applied as single intervention.

Discontinuation due to adverse events

There are no reports of discontinuation due to AEs in the submitted studies.

Post-marketing experience

Chlorhexidine has a well-characterised safety profile when used as recommended.

2.6.1. Discussion on clinical safety

Chlorhexidine has a well-known safety profile from over 60 years post-marketing experience and has been licensed for use in a variety of ways including as hand washes, preoperative body showering and skin disinfection, wound care and oral hygiene. Common formulations of chlorhexidine include aqueous and alcohol-based solutions, gels, and powders; all have been used topically on adult, infant and neonatal skin. The level of clinical exposure to chlorhexidine over this period helps to provide a very clear indication of the likely risks associated with using chlorhexidine in different patient groups.

The clinical safety data in support of this application consist of three large published community-setting randomised controlled trials in resource-poor settings which evaluated the use of 7.1% chlorhexidine digluconate liquid prepared by diluting a 20% chlorhexidine digluconate solution (4% chlorhexidine) [Mullany, 2006a; El-Arifeen, 2012; Soofi, 2012] and a published non-inferiority, randomised study comparing the performance of a 7.1% chlorhexidine digluconate (4% chlorhexidine) gel with 7.1% (4% chlorhexidine) solution [Hodgins, 2010].

Additionally, *in-vitro* antibacterial equivalence and skin irritancy studies have been conducted to bridge efficacy and safety data from the published studies of chlorhexidine digluconate 7.1 % (4% chlorhexidine) solution to the GSK chlorhexidine gel. Further evidence of the safety of chlorhexidine has been derived from the literature.

2.6.2. Conclusions on the clinical safety

Data from the large published community randomised trials together with the extensive post-marketing experience of chlorhexidine digluconate provide supporting evidence of its safety for its use in prophylaxis of omphalitis (umbilical cord infection) in newborn infants.

Known safety issues relating to the topical use of chlorhexidine products include skin irritation and systemic hypersensitivity reactions/ anaphylaxis. Other potential safety considerations relate to a risk of chemical burns in premature infants, systemic absorption and the presence of a trace impurity present in all chlorhexidine products: 4-chloroaniline (4-CA), which is associated with methaemoglobinaemia and a theoretical increased cancer risk.

The applicant acknowledges that there is a risk of skin reactions and chemical burns with use of chlorhexidine topical disinfectants in pre-term infants, more so in extremely pre-term infants. The applicant has presented evidence from clinical trials and from case reports that these risks are exposure related and can therefore be mitigated by limiting exposure as follows. This product does not contain alcohol and a single dose of CHX Gel for preterm infants born at <32 weeks gestation or weighing < 1500g is proposed. It is therefore considered acceptable not to exclude preterm infants born at <32 weeks gestation.

The applicant has provided further reassurance that the risk of methaemoglobinaemia following localised and short-term administration of CHX Gel, although uncertain, is considered to be low throughout the product shelf-life.

The theoretical lifetime cancer risk is minimal (approximately 5 per million).

The SmPC and PL have been updated with all appropriate cautionary warnings and are considered acceptable.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Anaphylaxis
Important potential risks	Chemical burns Methaemoglobinaemia associated with exposure to significant 4-CA levels
Missing information	None identified

Pharmacovigilance plan

No studies are ongoing or planned.

Risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Anaphylaxis	SPC section measures: Contraindicated for caregiver with known hypersensitivity to the product (4.3) Warnings and precautions for symptom recognition and advice to discontinue product when these are observed (4.4) Listed as undesirable effect (4.8).	None
Chemical Burns	SPC section measures: Dose reduction in pre-term infants and avoiding the use of occlusive dressings recommended (4.2) Warnings and precautions of risk and higher risk pre-term sub-population (4.4)	None
Methaemoglobinaemia associated with exposure to significant 4-CA levels.	Measures to minimise 4-CA in product throughout shelf-life SPC section measures: Dose reduction in pre-term infants recommended (4.2) Warnings and precautions of risk (together with signs and symptoms) and higher risk pre-term sub-population (4.4)	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The data generated by the clinical trials conducted with chlorhexidine and assessed by CHMP demonstrate that application of 7.1% chlorhexidine reduces overall mortality by more than 20% (between 20% and 38%) in newborn infants who are delivered in community or primary care centres in resource-limited settings. An early application of chlorhexidine within 24 hours after birth, as reported by one of the trials, contributed to a more favourable outcome. Moreover, the incidence of omphalitis is also importantly reduced (by 24% to up to 75%) in the chlorhexidine-treated neonates.

The bridging of the efficacy data from the solution to the gel was performed via a randomised, non-inferiority study comparing the rate of peri-umbilical colonisation 24 hours post application of the 4% gel with the 4% chlorhexidine aqueous solution. These data are also supported by the conducted *in vitro* antibacterial equivalence and skin-irritancy studies, which allow the bridging of efficacy and safety data generated with the chlorhexidine digluconate 7.1% (4% chlorhexidine) solution to the GSK CHX Gel.

Uncertainty in the knowledge about the beneficial effects

There was a statistically significant reduction in the incidence of moderate and severe omphalitis with multiple applications than with a single application, but no difference in overall mortality between the two groups. This can lead to some ambiguity in whether multiple or single application should be recommended, and this is reflected in the national guidelines of some countries.

Also, data on the use of chlorhexidine-containing products in premature infants (gestational age < 37 weeks) are limited. A literature review of the use of chlorhexidine in premature infants did not identify any specific studies of efficacy in this population for skin antisepsis or umbilical cord care. Given the mechanism of action, it is likely that the efficacy of a topically applied antiseptic product will be the same in very preterm (28 to <32 weeks) and extremely preterm infants (<28 weeks) as well as those born after 32 weeks gestation. In the Bangladesh study, some evidence of a greater benefit in preterm infants (< 37 weeks) was observed. While multiple applications in *premature infants* showed a trend towards a reduction in overall mortality, a statistically significant difference was however only shown with single application in this population.

There is less evidence of a beneficial effect with the use of chlorhexidine in hospital settings, although many studies analysed in different systematic reviews were conducted in developed countries, which may have led to differences in populations and healthcare practices compared to developing countries.

Lower chlorhexidine concentrations than those tested in the trials presented for assessment have also been investigated by other studies, but the numbers enrolled were substantially lower than the country-based studies, and no meaningful conclusions could be drawn.

Risks

Unfavourable effects

Known safety issues relating to the topical use of chlorhexidine products include skin irritation and systemic hypersensitivity reactions/ anaphylaxis. Although uncommon (≥1/1000 and <1/100), the most commonly reported adverse events for topically applied chlorhexidine are contact dermatitis and photosensitisation [Chapman, 2012]. Nevertheless, CHMP acknowledged that the proposed chlorhexidine gel formulation does not contain alcohol and that occlusive dressings are not recommended and agreed that the incidence of contact dermatitis with use of the chlorhexidine gel formulation for newborn umbilical cord cleansing is therefore expected to be low.

There have been isolated reports of anaphylaxis in a wide variety of medicinal products and devices containing chlorhexidine. The frequency following use of chlorhexidine gel is expected to be very rare because no anaphylaxis cases were reported in the four trials involving 30,247 newborns exposed to chlorhexidine digluconate 7.1% solution.

Uncertainty in the knowledge about the unfavourable effects

Other potential safety considerations relate to a risk of chemical burns in premature infants, systemic absorption and the presence of a trace impurity present in all chlorhexidine products: 4-chloroaniline (4-CA), which is associated with methaemoglobinaemia and a theoretical increased cancer risk.

Benefit-risk balance

Importance of favourable and unfavourable effects

The data provided demonstrate that application of 7.1% chlorhexidine gel reduces overall mortality in newborn infants who are delivered in community or primary care centres in resource-limited settings.

Known safety issues relating to the topical use of chlorhexidine products include skin irritation and systemic hypersensitivity reactions/ anaphylaxis. Other potential safety considerations relate to a risk of chemical burns in premature infants, systemic absorption and the presence of a trace impurity present in all chlorhexidine products: 4-chloroaniline (4-CA), which is associated with methaemoglobinaemia and a theoretical increased cancer risk.

The frequencies of the identified risks of skin irritation and anaphylaxis/hypersensitivity are expected to be rare and very rare, respectively and the potential risk of chemical burns is also expected to be very rare. The applicant has presented evidence from clinical trials and from case reports that risk of chemical burn is exposure related and can therefore be mitigated by limiting exposure. This product does not contain alcohol and a single dose of CHX Gel for preterm infants born at <32 weeks gestation or weighing < 1500g is proposed. It is therefore considered acceptable not to exclude preterm infants born at <32 weeks gestation.

The applicant has added an appropriate wording to the Product Information regarding chemical burns.

The available published data do not suggest that there would be any safety concerns if systemic absorption did occur.

The potential risk of methaemoglobinaemia is expected to be very rare. The proposed product is for topical application and for short-term use. The applicant has provided further reassurance that the risk of methaemoglobinaemia following localised and short-term administration of CHX Gel, although uncertain, is considered to be low throughout the product shelf-life. The SmPC and PL have been updated with appropriate cautionary warnings.

Benefit-risk balance

CHMP agreed that the benefit-risk balance for Umbipro in the prophylaxis of omphalitis (infection of the umbilical cord) in newborn infants is positive.

Discussion on the benefit-risk balance

Umbipro is exclusively intended for countries outside the European Economic Area, for the prophylaxis of omphalitis (umbilical cord infection) in newborn infants in the community. Data from the large published community randomised trials in combination with the extensive post-marketing experience of chlorhexidine digluconate provide supporting evidence of its favourable benefit / risk profile for this use.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Umbipro in the prophylaxis of omphalitis (infection of the umbilical cord) in newborn infants is favourable.

Conditions or restrictions regarding supply and use

Medicinal product not subject to medical prescription

Official batch release

The CHMP recommends that batch compliance control of individual batches be performed before release on

the market in third countries.

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The scientific opinion holder shall submit the first periodic safety update report for this product within 90 calendar days after the data lock point of 1 June 2017. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every year until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.