British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.2017.31

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 8th APS International PharmSci 2017

Enabling an Accelerated Development Path for Chlorhexidine Digluconate Gel 7.1% w/w for the Prevention of Omphalitis

L. Immins, N. Jibry, D. Hunt, K. Cheng, P. Chowdhury, C. Patel, S. Wilhelm, E. DeAngelis* P. Williams

GlaxoSmithKline R&D Ltd, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

ARTICLE INFO

Received: 06/04/2017
Accepted: 07/08/2017
Published: 11/07/2018

*Corresponding author. Tel.: +44 7818 527850
E-mail: elena.deangelis@gsk.com

KEYWORDS: chlorhexidine; gel; Article 58; acceleration

SUMMARY

In 2012, the United Nations (UN), identified chlorhexidine as a Life-saving Commodity and called for the development of a chlorhexidine product suitable for the prevention of omphalitis (umbilical cord infection) in developing countries. In response, GlaxoSmithKline (GSK) set out to develop a chlorhexidine digluconate 7.1% w/w gel, in partnership with Save the Children. The vision was to develop a gel which could pass a stringent regulatory review thereby assuring a safe, effective, and quality product. Review under the European Medicines Agency's (EMA) Article 58 pathway was pursued, with accelerated assessment granted. The regulatory dossier compiled literature-based evidence for clinical efficacy and safety, supplemented by GSK-generated *in-vitro* studies and a full CMC data package to support the quality. No new clinical trial data or *in vivo* non-clinical study data were submitted. A positive opinion from the EMA was received in 2016. The time from the initial UN call to EMA Positive Opinion was 3 years and 7 months.

INTRODUCTION

The United Nations Commission Report on Life-saving Commodities for Women and Children, identified chlorhexidine for newborn cord care as one of thirteen lifesaving commodities (United Nations, 2012). The newly cut umbilical cord is a common entry point for bacteria that can cause infection of the umbilical cord stump leading to neonatal sepsis and death. Umbilical cord infection (omphalitis) is most likely to occur in low income settings, primarily in developing countries in Africa and South Asia. There are significant gaps in access to this medicine due to limited awareness and demand.

In direct response to the UN call, GSK set out to rapidly develop a chlorhexidine digluconate 7.1% w/w gel, in partnership with Save the Children. Chlorhexidine is a key ingredient in Corsodyl™ a GSK oral healthcare product. The vision was to develop a chlorhexidine gel which could pass a stringent regulatory review thereby assuring a safe,
effective and quality product to fill gaps where there is no local manufacturing supply or insufficient supply due to quality or volume.

The formulation and manufacturing processes were to be designed to be as simple as possible with an open source approach to share formulation and manufacturing knowledge with local companies to enable them to make the gel.

MATERIALS AND METHODS

GSK Consumer Health and Pharma R&D divisions collaborated to utilise both the extensive product knowledge base already available, e.g. API

https://doi.org/10.5920/bjpharm.2017.31

degradation pathways and also their different experiences of speed and routes to market for a pharmaceutical product.

The antiseptic ingredient (chlorhexidine digluconate) was reformulated from a solution product into a gel in a 3g single-use laminate sachet. Pictorial instructions are used to help mothers and carers in low literacy settings to apply the gel correctly. A published chlorhexidine gel formulation was simplified and optimised to minimise formation of impurities, in particular 4-chloroaniline (4-CA) which has been shown to be genotoxic and carcinogenic in non-clinical studies. (CICAD 2003)

Efficacy is supported by three published community-based randomized controlled trials of chlorhexidine digluconate 7.1% solution in South Asia and a further non-inferiority study of chlorhexidine gel versus solution for antimicrobial efficacy (El-Arifeen S et al. 2012; Hodgins S, 2010; Mullany L et al. 2006; Soofi S et al. 2012). These data were supplemented by literature reviews of clinical and nonclinical safety information. Three *in vitro* tests were performed with the gel formulation: antibacterial equivalency (kill time and, substantivity) and a skin-irritancy study, to bridge efficacy and safety data from the published studies of chlorhexidine solution to the gel product.

In July 2013, the EMA in collaboration with the World Health Organisation (WHO), granted eligibility for the gel product to obtain a CHMP (Committee for Human Medicinal Products) Scientific Opinion through the Article 58 process. This allows the issuance of a Certificate of Pharmaceutical Product (CPP) by the EMA to support national Marketing Applications as required.

GSK worked with the EMA through the Scientific Advice process to agree the Clinical, Non-clinical, Quality and Regulatory strategy, including control of 4-CA and drug product stability data package. In September 2015, the EMA granted an accelerated assessment, reducing the review period to 150 days. Regulatory filing was submitted in October 2015.

In February 2016, a Managed Access (Compassionate Use) Programme was established in Bungoma county Kenya, in partnership with Save the Children to provide early access at the request of the Kenya Ministry of Health. The user acceptability study results will be used to advocate for national scale up in Kenya and help inform on use of chlorhexidine digluconate 7.1% products in other countries.

RESULTS AND DISCUSSION

GSK rapidly developed a high quality Chlorhexidine Digluconate 7.1% w/w gel with a 2 year shelf-life suitable for climatic regions where the product is intended (and according to WHO recommendations) and where the supply chain logistics can be challenging. The regulatory dossier compiled literature-based evidence for efficacy, clinical and nonclinical safety, supplemented by GSK-generated in *vitro* studies. No new clinical trial data or *in vivo* non-clinical study data were submitted. A CHMP positive opinion was achieved in April 2016 following EMA's Article 58 procedure with accelerated assessment. The time from the UN call to the EMA Positive Opinion was 3 years, 7 months.

CONCLUSIONS

GSK has developed Chlorhexidine Digluconate 7.1% w/w gel in a single-use sachet for prophylaxis of omphalitis. The path to approval was accelerated by: 1) availability of published and internal knowledge of chlorhexidine; 2) leverage of the expertise of different product development route from Consumer and R&D divisions ; 3) Engaging with the EMA through the Scientific Advice procedures; 4**)** use of published clinical trial data ; 5) accelerated EMA review of the Article 58 submission.

ACKNOWLEDGEMENTS

All authors are employees of GlaxoSmithKline Ltd.

REFERENCES

CICAD 2003: Concise International Chemical Assessment Document 48, 4-Chloroaniline

El Arifeen S., et al., 2012. Lancet 379: 1022–8.

Hodgins S., et al., 2010. Pediatric Infectious Diseases 29(11): 999-1003.

Mullany LC., et al., 2006. Lancet 367: 910–8.

Soofi S., et al., 2012. Lancet 379: 1029–36.

United Nations (UN) Commission Report on Life-saving Commodities for Women and Children, September 2012.

WHO Recommendations on Postnatal Care of the Mother and Newborn. October 2013