A.16 Hypochlorous acid – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☒ Not supportive of the proposal Justification (based on considerations of the dimensions described below): This Application refers to the addition of **hypochlorous acid** to the WHO Essential Medicines List in the categories of disinfection, antisepsis, and wound care. A similar Application was submitted in 2021. At that time the Expert Committee considered that 1) a separate listing for the proposed formulation of hypochlorous acid solution was not needed as it could be captured under the existing listing for 'chlorine-based compounds' and 2) the available evidence for its use as antiseptic and for wound decontamination was too limited to support the inclusion. The Expert Committee however welcomed future application including data from ongoing studies and a more comprehensive review of the literature. This Report discusses the assessment of the proposed evidence and information for **hypochlorous acid** as environmental disinfectant and topical agent for antisepsis and wound care separately. For the latter indication it focuses on the updated evidence submitted. **1. Environmental disinfectant** The Application argues the classification of hypochlorous acid under the chlorine-based compounds is not appropriate, given the different characteristics in safety profile and disinfectant efficacy. Apparently, there is a variable terminology surrounding chlorine solutions in the literature, sodium hypochlorite and hypochlorous acid are frequently interchanged despite the differences. Often, they are generally referred to as chlorine solutions. Chlorine-based disinfectants commonly used in healthcare and clinical settings include sodium hypochlorite (bleach) that contains hypochlorite (OCl-) as the dominant chlorine species present in solution. The relationship between hypochlorite ions and hypochlorous acid is pH dependent Ref: https://doi.org/10.29392/001c.84488 Therefore, this Reviewer is in favour of an explicit listing of **hypochlorous acid** as disinfectant to contribute to the understanding of the differences between hypochlorite and hypochlorous acid. Accurate terminology may help prevent harm from incorrect in-vivo use of hypochlorite (bleach), that should be used only for surface disinfection. **2. Topical application for antisepsis and wound care** Hypochlorous acid appears to be a safe and effective antiseptic with a broad activity against a wide range of pathogens and has an acceptable safety profile. It meets the essential requirements for a topical antiseptic agent, e.g., biocidal activity, broad spectrum of action (gram +, - viruses, spores, fungi), rapid action and long persistence of the activity, non-toxicity for humans at the concentrations of use, harmlessness on the materials to be treated, ease of application, and cost-effectiveness of management. Moreover, it has good chemical stability, it does not have irritating or sensitizing effects or affect the healing process. Recent advances in manufacturing have improved standardization of the product. Hypochlorous acid can be a suitable option in several surgical settings (oralmaxillofacial, dermatologic and plastic procedures, intraperitoneal wound care), and in the management of chronic wounds. However, the evidence supporting these considerations is relatively limited and derived from small and heterogeneous studies. Unfortunately, the Application does not provide an updated comprehensive review of clinical studies that could adequately inform the decision-making process to list hypochlorous acid as antiseptic and for wound care. Therefore, this Reviewer feels **hypochlorous acid** cannot be included as antiseptic agents this time but encourage the submission of a future application reporting a **structured, comprehensive summary of the clinical evidence and its critical appraisal** for these indications and across the different clinical settings.

Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? Chlorine based compound are listed as disinfectants since 1997 (section revised in 2021) Disinfectants Local > Topical > Powder: 0.1% available chlorine for solution Local > Topical > Liquid: 0.1% available chlorine for solution Local > Topical > Solid: 0.1% available chlorine for solution Topical antiseptics are also listed, including chlorhexidine, alcohol-based hand rub, povidone iodine, glutaraldehyde. No clear reference to wound infection management is specified (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? The Applications lists several publications on the effect of hypochlorous acid as disinfectant and topical antiseptic, from laboratory studies to clinical trials and consensus papers. The Application mentioned 12 RCTs assessing hypochlorous acid solution for wound infectious management (six in people with diabetes, four in surgical setting, one in people with chronic wound, one in people in dialysis). Unfortunately, the Application does not report a clear summary of the evidence and a critical appraisal of its certainty, making difficult the understanding of the actual efficacy/effectiveness of the hypochlorous acid across indications. There is no information on how they were retrieved and selected it is difficult to firmly concluded on the comprehensiveness of the Application. Given the broad range of application of hypochlorous acid as topical antiseptic agent, it is likely that other important studies could have been mentioned. Published reviews assessed the role of hypochlorous as antiseptic and anti-inflammatory agent in pre and peri surgery procedures and in post-procedures, including post-sutures, as a wound healing agent. Hypochlorous acid appears to be highly active against Staphylococcus aureus and Pseudomonas aeruginosa, both regularly implicated in both acute and chronic wound infections. A consensus review published in 2018 reported the following summary table suggesting a possible benefit in several medical areas	☐ Yes ☒ No ☐ Not applicable

Table 8. Summary of clinical study findings for the combination NaOCl/HOCl

Type of wound	Comparison	Result	Study design	Sample size, *n*	Year
Explorative laparotomy/ peritonitis	NaOCl/HOCl vs. NaCl	OCl: significant reduction of fever and prevention of SSI	RCT	50/50	2013 [150]
Diabetic foot ulcers, VLU, burns	NaOCl/HOCl vs. PVP-I	OCl: faster granulation and epithelialization, faster reduction of wound size, reduction of surrounding edema and erythema, better cosmetic results in burn wounds; PVP-I: minute skin irritation and pain in burns	RCT	100/100	2011 [304]
Chronic wounds, SSI	NaOCl/HOCl vs. PVP-I	OCl: significant wound size reduction, fewer persisting infections due to *P. aeruginosa*, *S. aureus*, and *Klebsiella* spp.	RCT	50/50	2011 [305]
Diabetic foot ulcers	NaOCl/HOCl vs. PVP-I	OCl: significantly better wound healing, control of infection, significantly more interventions in the PVP-I study section	RCT	20/20	2010 [306]
Chronic wounds	NaOCl/HOCl vs. PVP-I	OCl: significant wound size reduction, better control of microbial colonization; was well tolerated	RCT	15/15	2009 [307]
Diabetic wounds	NaOCl/HOCl vs. NaCl (soaked gauze)	OCl: significantly reduced hospitalization and wound size, improvement in wound score	Blinded RCT	50/50	2007 [278]
Diabetic foot ulcers	NaOCl/HOCl vs. PVP-I	OCl: significant reduction of malodor, significant reduction of soft tissue infection, improved granulation, lower occurrence of erythema	Blinded RCT	21/16	2007 [308]
Diabetic foot ulcers	NaOCl/HOCl vs. PVP-I	OCl: reduced treatment time	RCT	110/108	2005 [309]
Burns	NaOCl/HOCl vs. Ag	OCl: 11% reduction in use of antibiotics, 50% reduction in hospitalization	Retrospective cohort study	64/64	2005 [310]
SSIs	NaOCl/HOCl vs. PVP-I	OCl: significantly reduced hospitalization and reduction of pain	Retrospective cohort study	46/42	2001 [311]

Table 10. Summary of clinical findings for wound antiseptics

Criteria	NaOCl/HOCl	OCT	PHMB	PVP-I
Antimicrobial efficacy	Yes	Yes	Yes	Yes
Improvement of wound healing	Yes	No inhibition	Yes	Partly inhibition
Peritoneal lavage in septic peritonitis	Possible	Contraindicated	Contraindicated	Contraindicated
Applicability of CNS tissue	Possible	Contraindicated	Contraindicated	Toxic [316]
Applicability on cartilage	Possible	Contraindicated	Only at <0.005%	Yes
Superior to				
Ag^+	Tendentially better	Significantly better	Significantly better	Tendentially better
PVP-I	Significantly better	Tendentially better	Significantly better	–
CHD	No studies	No studies	Significantly better	No studies
Prevention of SSI	Possible	No studies	Effective	Tendentially better

The review concluded that due to the paucity of clinical studies, the selection of wound antiseptics is based on both preclinical and clinical studies of nonuniform research quality and design. From the literature available, it is not possible to firmly conclude on the added benefit of hypochlorous acid over other antiseptics.

Ref: https://doi.org/10.1159/000481545

Does adequate evidence exist for the safety/harms associated with the proposed medicine? Hypochlorous acid appears to be a safe component of wound care for a wide range of dermal lesions, including chronic non-healing wounds.	☒ Yes	☐ No	☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☐ Yes	☐ No	☒ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Careful manufacturing and storage is important for maintaining efficacy and avoid the introduction of contaminants that may not be optimal for either environmental or topical applications.	☐ Yes	☒ No	☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? No data on comparative cost and effectiveness are included in the Application.	☐ Yes	☒ No	☐ Not applicable

However, costs are low and since 2021 when the previous application for hypochlorous acid inclusion was submitted, costs of production have been highly reduced and multiple local manufacturing facilities have been established even in remote settings	
Is the medicine available and accessible across countries?	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval? US FDA: Approved for disinfection of food-contact surfaces, high-level disinfection, sterilization, and wound care applications. European Union: Approved in some formulations as a Class III medical device for wound management. Hypochlorous acid-based antiseptic solutions are commercially available at different concentrations: the 0.05% one is effective for the antisepsis of injured skin, the 0.1% one is indicated for the antisepsis of intact skin. Hypochlorous acid is active against Gram positive and negative bacteria, mycobacteria, fungi, lipophilic and hydrophilic viruses and spores. Mycobacteria or clostridium tetani may require higher concentration as well as longer exposures. Wound care solutions cleared for the US market by FDA range from 100-200 ppm of oxidative titratable chlorine. A preparation of hypochlorous acid approved as a Class III medical product for wound care in the European Union contains no more than 200 ppm oxidative titratable chlorine.	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable