

A.18	Hypochlorous Acid for disinfection, antiseptis, and wound care
<p>Does the application adequately address the issue of the public health need for the medicine?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Cleaning and disinfection of environmental surfaces in the health care setting are essential elements of effective infection prevention programs.</p> <p>Cleaning helps to remove pathogens or significantly reduce their load on contaminated surfaces and is an essential first step in any disinfection process. Cleaning with water, soap (or a neutral detergent) and some form of mechanical action (brushing or scrubbing) removes and reduces dirt, debris and other organic matter such as blood, secretions and excretions, but does not kill microorganisms. Chemical disinfectant, such as chlorine or alcohol, should be applied after cleaning to kill any remaining microorganisms. An ideal disinfectant and sanitizer must be nontoxic to surface contact, noncorrosive, effective in various forms, and relatively inexpensive.</p> <p>Antiseptics are chemical agents applied to the skin to reduce the microbial count and reduce the risk of wound infections. Surgical wounds and chronic wounds related to diabetes mellitus, venous stasis, peripheral vascular diseases, and pressure ulcerations may be a favourable niche for bacterial colonization and infection. Infection in chronic wounds starts with contamination, then colonization and critical colonization take place before an infection form. Wound infection is a common complication of wounds. It leads to delays in wound healing and increases the risk of loss of limb and life. Implementation of effective strategies to prevent, diagnose and manage, is important in reducing mortality and morbidity rates associated with wound infection. The application of a cleansing solution has the potential to disrupt biofilm and kill planktonic bacteria and other organisms and prevent further contamination and cross infection.</p> <p>Using topical antiseptics to treat superficial skin lesions with mild infections is advisable also to avoid the use of antibiotics. For instance, the WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention suggested that antibiotic incisional wound irrigation before closure should not be used because this practice is associated with an unnecessary risk of antimicrobial resistance. Povidone-iodine solutions can provide a significant benefit in the irrigation of the incisional wound compared with irrigation with a saline solution (Allegranzi 2016).</p>
<p>Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.</p>	<p>The Application regards the inclusion of Aqueous Hypochlorous Acid in the Model List as environmental disinfectant and topical application for antiseptis and wound care.</p> <p>For increase the clarity of this report, this Reviewer tried as far as possible to describe the assessment of the proposed evidence and information separately for the two areas of use.</p> <p>1. Environmental disinfectant</p> <p>Chlorine disinfectants are listed since 1997.</p> <p>Chlorine-releasing compounds: The EMLc Subcommittee endorsed the inclusion of chlorine base compound (with a square box) as a disinfectant on the core list of the Model List. The Subcommittee recognized that the disinfectants were not medicines per se, but the importance of a clean environment where children are treated was seen as a priority and the inclusion of this section was to emphasize the importance</p>

	<p>of infection control (https://list.essentialmeds.org/?indication=610).</p> <p>2. Topical application for antiseptics and wound care</p> <p>Other topical antiseptics have been listed in the Model List in the last years, including chlorhexidine, alcohol-based hand rub, povidone iodine, glutaraldehyde. No clear reference to wound infection management is included.</p>
<p>Have all important studies and all relevant evidence been included in the application?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p>1. Environmental disinfectant</p> <p>Several studies are listed and described in the Application, including data from laboratory evaluations of hypochlorous acid against a range of pathogenic organisms. There is no information on how they were retrieved and selected. A thorough evaluation of the comprehensiveness and representativeness of these studies go beyond the expertise of this Reviewer.</p> <p>2. Topical application for antiseptics and wound care</p> <p>Several studies are listed and described, including bench research, randomised controlled trials (RCTs), reviews, etc. Given the broad range of application of hypochlorous acid as topical antiseptic agent, it is likely that other important studies could have been mentioned. Again, as there is no information on how they were retrieved and selected it is difficult to firmly concluded on the comprehensiveness of the Application.</p>
<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).</p> <p>1. Environmental disinfectant</p> <p>Overall, hypochlorous acid appears to be an active disinfectant for the use in contaminated environment given its action against a variety of common pathogens present in a healthcare or community environment.</p> <p>Aqueous solutions of hypochlorous acid approved for disinfection contains:</p> <ul style="list-style-type: none"> • up to 200 ppm of oxidative titratable chlorine (European Union) • 180-460 ppm oxidative titratable chlorine (United States) <p>According to the WHO Interim Guidance Document on “cleaning and disinfection of environmental surface in the context of Covid-19” hypochlorite is effective against rotavirus at a concentration of 0.05% (500 ppm), however, higher concentrations of 0.5% (5000 ppm) are required for some highly resistant pathogens in the healthcare setting such as <i>Candida auris</i> and <i>Clostridium difficile</i>.</p> <p>Therefore, hesitancy exists in the use of hypochlorous acid in healthcare environment, because many antimicrobial resistant/contact transmissible pathogens which will require much higher concentrations for effective inactivation.</p>

2. Topical application for antiseptics and wound care

Hypochlorous acid, a naturally occurring molecule produced by the immune system, is highly active against bacterial, viral, and fungal microorganisms. Neutrophils, eosinophils, mononuclear phagocytes, and B lymphocytes produce hypochlorous acid in response to injury and infection through the mitochondrial membrane-bound enzyme known as “respiratory burst nicotinamide adenine dinucleotide phosphate oxidase”. Hypochlorous acid selectively binds with the unsaturated lipid layer and subsequently disrupts cellular integrity. Hypochlorous acid is a powerful oxidizing agent. Moreover, hypochlorous acid is active against biofilm and increases oxygenation of the wound site to improve healing. Natural hypochlorous acid is unstable; through technology, it can be stabilized into an effective topical antiseptic agent (Block 2020, Wang 2007).

Between pH levels of 3 and 6, the predominant species is hypochlorous acid that has maximal antimicrobial properties. Controlled manufacturing processes allow production of stable solutions with high purity.

Hypochlorous acid-based antiseptic solutions are commercially available at different concentrations: the 0.05% one is effective for the antiseptics of injured skin, the 0.1% one is indicated for the antiseptics 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.

The role of hypochlorous acid was evaluated 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 reported the following summary table suggesting a possible benefit in several medical areas (Kramer 2018).

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

Type of wound	Comparison	Result	Study design	Sample size, Year <i>n</i>
Explorative laparotomy/ peritonitis	NaOCl/HOCl vs. NaCl	OCI: significant reduction of fever and prevention of SSI	RCT	50/50 2013 [150]
Diabetic foot ulcers, VLU, burns	NaOCl/HOCl vs. PVP-I	OCI: 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	OCI: significant wound size reduction, fewer persisting infections due to <i>P. aeruginosa</i> , <i>S. aureus</i> , and <i>Klebsiella</i> spp.	RCT	50/50 2011 [305]
Diabetic foot ulcers	NaOCl/HOCl vs. PVP-I	OCI: 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	OCI: 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)	OCI: significantly reduced hospitalization and wound size, improvement in wound score	Blinded RCT	50/50 2007 [278]
Diabetic foot ulcers	NaOCl/HOCl vs. PVP-I	OCI: 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	OCI: reduced treatment time	RCT	110/108 2005 [309]
Burns	NaOCl/HOCl vs. Ag	OCI: 11% reduction in use of antibiotics, 50% reduction in hospitalization	Retrospective cohort study	64/64 2005 [310]
SSIs	NaOCl/HOCl vs. PVP-I	OCI: significantly reduced hospitalization and reduction of pain	Retrospective cohort study	46/42 2001 [311]

PVP-I: polyvinyl-pyrrolidone iodine, SSI: surgical site infections.

From the literature available, it is not possible to firmly conclude on the added benefit of hypochlorous acid over other antiseptics. 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 uncertain quality. It is suggested that polihexanide and hypochlorite are superior to PVP-I for the treatment of contaminated acute and chronic wounds. For peritoneal lavage or rinsing of other cavities with a lack of drainage potential or when the risk of central nervous system exposure exists, hypochlorite is the antiseptic of choice.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

The Application does not clearly report evidence in diverse settings.

There is an increased interest for the use of hypochlorous acid in pediatric wound management and low concentration nasal irrigation.

The Application reports a review of hypochlorous acid as a peritoneal lavage to prevent post-surgical infections after perforated appendicitis in children, that reported no evidence of toxicity and they found a statistically significant reduction in surgical site infections with hypochlorous acid (Kubota 2015).

A randomized, prospective, active-controlled study on 26 pediatric patients with rhinosinusitis suggested that nasal irrigation with hypochlorous acid is an effective adjuvant treatment compared to isotonic normal saline (Cho 2016).

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?

- Yes
 No
 Not applicable

Comments:

1. Environmental disinfectant

	<p>There are reports of incidents following exposure to relatively high pH, crude formulations (>6.5) containing mixed oxidants, including hypochlorite, resulting from poorly controlled manufacturing processes. Similar problems may arise when modern hypochlorous acid formulations are deliberately pH-adjusted into the neutral or higher zone. Eye and skin inflammation and respiratory irritation are common with hypochlorite (bleach), which can be present at levels of 30% or more in hypochlorous acid solutions made or adjusted to pH 7.</p> <p>According to the Application, pure hypochlorous acid formulations at a label concentration of 180 ppm does not increase the risk of environmental contamination. Moreover, its use appears to be safer than other chlorine-based disinfectants (i.e., bleach): it does not require personal protective equipment, it can be stored with no hazardous materials protocol, and can be disposed of with no risk of generating a toxic waste stream.</p> <p>It should be noted that the WHO Interim Guidance Document on “cleaning and disinfection of environmental surface in the context of Covid-19” strongly recommended against the use of spray or fogging of disinfectants because they may result in serious health effects when applied in an occupied environment.</p> <p style="text-align: center;">2. Topical application for antiseptics and wound care</p> <p>Hypochlorous acid appears to be a safe component of wound care for a wide range of dermal lesions, including chronic non-healing wounds.</p> <p>The Application states that there are no reports of adverse reactions to topical applications by these methods based on the US EPA’s Toxicology Database DSSTox, the US CDC Toxic Substances and Disease Registry, nor at either the Development and Reproductive Toxicology Database, or the European Bioinformatics Institute of EMBL.</p> <p>Studies on human or animals did not report biological toxicity or toxicity due to inhalation or irritation or other type of toxicities. In terms of the safety and toxicity owing to the potential direct contact with ocular, skin and respiratory systems, stabilised hypochlorous acid has been found to be non-irritating (rabbit eye) and non-sensitising (guinea pig) in animal models.</p> <p>In general, 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.</p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>

<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p>1. Environmental disinfectant</p> <p>Hypochlorous acid could have a potential as environmental disinfectants, given its acceptable safety profile and low costs.</p> <p>However, its activity against transmissible pathogens commonly present in the healthcare facilities is not fully defined. Moreover, in some situations it is not completely defined the added value of using antimicrobials over optimal manual cleaning processes alone with clean water, detergents applied with manual friction.</p> <p>2. Topical application for antiseptis and wound care</p> <p>Overall, the hypochlorous acid appears to meet 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.</p> <p>Moreover, the compound has a good chemical stability, it does not have irritating or sensitizing effects or affect the healing process.</p> <p>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 wound such as bedsores and venous leg ulcers.</p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>1. Environmental disinfectant</p> <p>The overall quality of the evidence is judged to be low.</p> <p>Results from environmental cleaning studies are in general difficult to generalise and prone to bias (Leas 2015). Often there is a gap between appropriate use of surface cleaning/disinfection agents in studies and practical implementation in real-world settings. Manufacturers typically provide recommendations for proper use of their products, but most studies do not report thoroughness of cleaning or adherence to disinfectant contact time. Surface disinfection efficacy estimates are strongly influenced by each study's experimental conditions. If studies do not ensure adequate application and contact time, results may be biased. Conversely, if study results reflect a product's optimal use, failure to adhere to appropriate product application and contact time in practice may lead to suboptimal outcomes.</p> <p>Moreover, many confounding factors, including operator behaviour, hand hygiene, etc. may contribute to biased estimates.</p> <p>2. Topical application for antiseptis and wound care</p> <p>Although a formal grading was not possible, given the heterogeneity of the studies proposed, this Reviewer judges the overall quality of the evidence to be low. A variety of small clinical trials were conducted in several different indications providing evidence on efficacy but the benefit over available alternatives is not fully defined.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>

<p>Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The hypochlorous acid formulation proposed in this Application has been evaluated by regulatory agencies, healthcare institutions, professional organizations, independent laboratories, and academic institutions in more than 50 countries.</p> <p>1. Environmental disinfectant</p> <p>Hypochlorous acid solutions are registered for commercial use in the US, European Union, Canada, Association of Southeast Asian Nations (ASEAN), and Australia.</p> <p>Hypochlorous acid solutions are included in the WHO list of coronavirus-effective biocides.</p> <p>In the US, hypochlorous acid solutions are approved for:</p> <ul style="list-style-type: none"> • COVID-19 disinfection • drinking water and as a no-rinse food sanitizer • use for food-contact surfaces in public eating places, dairy processing equipment, food-processing equipment, and utensils • high level disinfection and sterilization of medical instruments, including those for use at critical (i.e., sterile) sites. <p>2. Topical application for antiseptics and wound care</p> <p>In the European Union Wound irrigation solutions containing antimicrobial agents are considered borderline products (medical device with an ancillary antimicrobial action). Hypochlorous acid is approved as a Class III medical product.</p> <p>Solutions of comparable composition are approved for topical uses within countries in Asia, Latin America, and the Middle East.</p> <p>Several branded aqueous hypochlorous acid formulations have been approved by the US FDA for topical use in wound management.</p>
<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Cleaning and disinfection of environmental surfaces in the context of COVID-19 https://www.who.int/publications/i/item/cleaning-and-disinfection-of-environmental-surfaces-in-the-context-of-covid-19</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>The Application reports that the current hypochlorous acid product cost at scale is about 2 US dollar per wholesale liter (0.002 US dollar per mL) at the manufacturing facility, with small regional variations.</p> <p>No other information on costs is reported.</p> <p>The current price is lower than that reported in a previous submission (inclusion of a proprietary electrolytically generated hypochlorous acid formulation ElectroCyn 2017: US\$ 5.52 per wholesale liter) and similar to alternatives such as povidone iodine and chlorhexidine (MSH International Drug Price Indicator Guide).</p> <p>Local production may be important to guarantee the availability of hypochlorous acid in disadvantage settings.</p>

Any additional comments	In 2017, the inclusion of hypochlorous acid solution and hydrogel as a wound disinfectant and in wound management was not recommended based on low-quality or inadequate evidence.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	<p>1. Environmental disinfectant</p> <p>Based on the assessment, this Reviewer is of the opinion that - in principle - hypochlorous acid can be recommended for inclusion in the Model List as disinfectant. The Expert Committee should consider whether its listing can be recommended now or should be postponed when data from current ongoing R&D project evaluating its use in hospital settings will be available.</p> <p>2. Topical application for antiseptics and wound care</p> <p>Based on the assessment, this Reviewer is of the opinion that the inclusion of hypochlorous acid solution as antiseptic and wound care can be recommended (0.05% on damaged skin, 0.1% on non-damaged skin).</p> <p>Branded and locally prepared hypochlorous acid solutions may be recommended, providing that they meet quality requirements for purity, potency, stability.</p>
References (if required)	<p>Allegranzi B, Zayed B, Bischoff P, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. <i>Infect Dis</i> 2016; 16: e288–303.</p> <p>Block MS and Rowan BG. Hypochlorous Acid: A Review <i>J Oral Maxillofac Surg</i>. 2020 78:1461-1466.</p> <p>Cho HJ, Min HJ, Chung HJ, et al. Improved outcomes after low-concentration hypochlorous acid nasal irrigation in pediatric chronic sinusitis. <i>Laryngoscope</i>. 2016;126(4):791-5.</p> <p>Gold MH, Andriessen A, Bhatia AC, et al. Topical stabilized hypochlorous acid: The future gold standard for wound care and scar management in dermatologic and plastic surgery procedures. <i>J Cosmet Dermatol</i>. 2020 Feb;19(2):270-277.</p> <p>Leas BF, Sullivan N, Han JH, et al. Environmental Cleaning for the Prevention of Healthcare-Associated Infections [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Aug. (Technical Briefs, No. 22.) Summary and Implications. Available from: https://www.ncbi.nlm.nih.gov/books/NBK316166/</p> <p>Kramer A, Dissemmond J, Kim S, et al. Consensus on Wound Antisepsis: Update 2018. <i>Skin Pharmacol Physiol</i> 2018;31:28–58.</p> <p>Kubota A, Goda T, Tsuru T, Yonekura T, Yagi M, Kawahara H, et al. Efficacy and safety of strong acid electrolyzed water for peritoneal lavage to prevent surgical site infection in patients with perforated appendicitis. <i>Surg Today</i>. 2015;45(7):876-9.</p> <p>Wang L, Bassiri M, Najafi R, et al: Hypochlorous acid as a potential wound care agent: Part I. Stabilized hypochlorous acid: A component of the inorganic armamentarium of innate immunity. <i>J Burns Wounds</i> 2007;6:e5</p>