Hypochlorous acid

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 15. Antiseptics and disinfectants > 15.1. Antiseptics

EMLc | Codes ATC: D08AX07

Indication	Hypochlorite Code ICD11: XM02H1
Type de médicament	Chemical agent
Type de liste	Liste de base (EML) (EMLc)
Formulations	Solution (aqueous): containing hypochlorous acid ≥ 150 parts per million
Historique des statuts LME	Demande refusée en 2025 (TRS 1064)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Hypochlorous acid

Recommandation du comité d'experts

The Expert Committee noted that the current application was a slightly modified version of an application for hypochlorous acid solution submitted by Briotech, Inc. in 2021. The Committee noted that no new evidence of benefits and harms of hypochlorous acid solution was presented, only the evidence already evaluated by the 2021 Expert Committee. The Committee recalled the recommendations of the 2021 Expert Committee, and considered that in the absence of new evidence, it was not possible to reach different conclusions. The Expert Committee did not recommend the inclusion of hypochlorous acid solution for topical use in antisepsis and wound care because of inconclusive evidence for benefit. In reviewing the case, the Committee agreed that an independent listing for hypochlorous acid solution as a disinfectant, separate to the existing listing for chlorine-based compound, would be beneficial to enhance understanding of differences between hypochlorite products and hypochlorous acid. The Expert Committee therefore recommended that an explicit listing for hypochlorous acid solution as an environmental disinfectant be included on the EML and EMLc to aid differentiation between hypochlorite and hypochlorous acid products.

Contexte

Hypochlorous acid solution and hydrogel were considered for inclusion on the Model Lists for use in wound management in 2017. The Expert Committee did not recommend listing because of inadequate evidence, noting that the quality of the evidence presented in the application for the solution formulation was uncertain and that no evidence was presented for the hydrogel formulation (1). An application for the inclusion of hypochlorous acid solution on the Model Lists for indications of disinfection, antisepsis and wound care (submitted by Briotech Inc., a manufacturer of hypochlorous acid products) was considered by the Expert Committee in 2021 (2). The current application appears to be modified version of the 2021 application. In consideration of the 2021 version of the application, the Expert Committee noted that recommendations for chlorine-based products, including hypochlorite formulations, are included in the 2020 WHO guidance on cleaning and disinfection of environmental surfaces in the

context of coronavirus disease 2019 (COVID-19). Liquid, solid or powdered hypochlorite-based formulations dissolve in water to create a dilute aqueous chlorine solution in which the undissociated hypochlorous acid is the active antimicrobial compound. The Committee noted that the Model Lists already listed chlorine-based compounds as disinfectants (Section 15.2), with a square box intended to indicate that various formulations could be considered acceptable alternatives for national selection and use. However, the listing at that time did not specify the characteristics of the alternative formulations. In consideration of a separate application to the 2021 meeting, in which square box listings in the EML and EMLc were reviewed, the Expert Committee recommended that the listing for chlorine-based compounds should be amended to provide greater clarity and guidance for countries. This recommendation resulted in liquid, powder and solid chlorine-based compounds of 0.1% available chlorine (for solution) being specified in the listing as alternatives available for national selection and use. Therefore, the Committee considered that a separate listing of hypochlorous acid solution as a disinfectant was not necessary, as this product would be captured under the amended listing for chlorine-based compounds. With regard to hypochlorous acid for antisepsis, the Committee noted that it appeared to be effective, with a broad activity against a wide range of pathogens, and it had an acceptable safety profile. Recent advances in manufacturing have improved standardization of the product. However, the evidence supporting these considerations was relatively limited and derived from small and heterogeneous studies. The Committee noted that ongoing studies had the potential to better clarify the advantages of hypochlorous acid and would inform a future consideration of this product for inclusion on the Model Lists. The Committee therefore did not recommend the inclusion of hypochlorous acid for antisepsis and wound decontamination in 2021 but advised that it would welcome a future application with data from ongoing studies and a more comprehensive review of the literature.

Pertinence pour la santé publique

The public health relevance of disinfectant and antiseptic interventions are well recognized. They contribute to ensuring appropriate infection prevention and control measures and can contribute towards combatting antimicrobial resistance.

Bénéfices

No new evidence of the benefits of hypochlorous acid solution was presented in the current application compared with the 2021 application. The following summary is reproduced from the technical report of the 2021 Expert Committee meeting (2). Disinfection An in vitro study showed anti-prion activity of hypochlorous acid solution using both intracerebral infectivity of treated prions of scrapie and with an in vitro fluorescent chemistry method showing efficacy against bovine spongiform encephalopathy, Creutzfeldt–Jakob disease and chronic wasting disease prions (3). Efficacy was shown to reach a log removal value of almost 6 after exposures of 60 minutes at room temperature. Log removal values of up to 3–4 were achieved with 5 minutes of contact with hypochlorous acid. Efficacy was also demonstrated against Bacillus spores. A retrospective, single-institution cohort study evaluated the efficacy of universal skin decolonization using mupirocin and hypochlorous acid solution to decrease health-care associated methicillin-resistant staphylococcus aureus (MRSA) infections in patients admitted to a burn intensive care unit in a tertiary care community hospital (4). Global MRSA infection rates per 1000 patient days were 7.23 pre-intervention and 2.37 post-intervention (incidence rate ratio 0.328, 95% confidence interval (CI) 0.167 to 0.646). The patients without universal decolonization had 3.05 times higher risk of acquiring an MRSA infection than those with universal decolonization. No complications were noted from use of hypochlorous acid solution for skin decolonization. An in vitro study to determine the efficacy of exposure to a pure hypochlorous acid solution for inactivation of high-risk human papillomavirus (HPV 16 and 18) found hypochlorous acid to be a highly effective disinfectant including with short contact times (5). All hypochlorous acid treatment times produced > 99.99% reduction in infectivity of HPV16 and HPV18, comparable to the efficacy of 0.87% sodium hypochlorite. Antisepsis A randomized controlled trial with 111 patients on intraperitoneal dialysis evaluated the efficacy and safety of a super-oxidized solution versus povidone-iodine following catheter placement in reducing the frequency of dialysis-associated infections (6). After 8 weeks of follow-up, 24.6% of the povidone-iodine group had experienced catheter-related infections compared with 5.6% in the super-oxidized solution group ($P < 0.05$). Additionally, the mean time for resolution of infection in the povidone-iodine group was 12 days compared with 4 days in the super-oxidized solution group ($P < 0.05$). An in vivo and vitro study assessed the effectiveness of a hypochlorous acid-based wound cleanser compared to other cleansers (povidone-iodine and chlorhexidine) in disrupting MRSA and Pseudomonas aeruginosa biofilms. The study also evaluated bioburden reduction of venous stasis wounds by the different cleansers (7). All the agents tested significantly neutralized MRSA and P. aeruginosa biofilms compared with saline control. Undiluted hypochlorous acid was significantly less cytotoxic than 1% and 10% povidone-iodine and chlorhexidine wound solution. No significant difference was seen in bacterial reduction in wounds after treatment with

hypochlorous acid for any type of bacteria examined. In wounds treated with hypochlorous acid or chlorhexidine, similar percentage reductions were observed in bacterial colony-forming units from pre-cleansing levels when plated on tryptic soy, MacConkey, streptococcal and mannitol salt agar plates. Plates treated with chlorhexidine showed greater bacterial reduction on non-selective and gram-negative agars, whereas plates treated with hypochlorous acid showed greater bacterial reduction in Streptococcus-selective agars. A randomized controlled trial in 80 patients with peritonitis compared 1-hour gastric lavage with intraperitoneal lavage with a super-oxidized solution after surgery (8). Purulent discharge occurred in 20.0% of patients receiving super-oxidized solution lavage versus 52.5% of patients receiving saline lavage ($P < 0.01$). The incidence of burst abdomen in patients receiving the super-oxidized solution lavage was significantly lower than those receiving saline lavage (27.5% versus 47.5%; $P < 0.05$). A prospective randomized trial of 178 patients compared the effectiveness of a neutral pH super-oxidized hypochlorous acid solution irrigation and povidone-iodine irrigation in reducing the incidence of sternotomy wound infection following coronary artery bypass graft surgery (9). Sternotomy wound infection was reported in 5.7% of patients in the hypochlorous acid group and 15.6% of patients in the povidone-iodine group ($P < 0.033$). A randomized study of 100 patients undergoing exploratory laparotomy for peritonitis compared intraoperative peritoneal lavage with a super-oxidized solution and normal saline (10). Surgical site infection occurred in 14% of patients receiving super-oxidized solution lavage versus 40% of patients receiving saline lavage ($P = 0.003$). Two patients in the super-oxidized solution lavage group died, compared with eight in the saline lavage group. Wound care A randomized trial of 60 patients compared the efficacy of hypochlorous acid versus povidone-iodine as a wound-care agent in septic traumatic wounds (11). Outcome measures for wound pain (no pain at day 14), odour (no odour at day 14), discharge (serous discharge at day 14) and bacterial count (reduction in day 14 quantitative count) all significantly favoured the hypochlorous acid group. At day 14, 90% of the group treated with hypochlorous acid had wounds ready for surgical reconstruction, compared with 0% in the povidone-iodine group. A randomized trial of 60 patients compared the efficacy of dressings with hypochlorous acid and povidone iodine in the management of infected diabetic ulcers (12). The mean change in ulcer area was significantly higher in patients treated with hypochlorous acid dressings compared with povidone-iodine dressings (2215 mm2 versus 1641 mm2, $P = 0.024$). Similarly, the mean percentage reduction in ulcer area in patients receiving hypochlorous acid dressings was significantly higher (58.9% versus 40.9%, $P = 0.024$). A randomized, prospective, multicentre, open-label pilot study tested the efficacy of topical hypochlorous acid for wound care versus oral levofloxacin versus combined therapy in 67 patients with mild diabetic foot infections (13). The clinical success rate 14 days after completion of therapy (test of cure) for patients treated with hypochlorous acid alone was 93.3% versus 56.3% for levofloxacin + saline-treated patients. The study was not statistically powered, but the high clinical success rate (93.3%) and the p-value ($P = 0.033$) suggest a meaningful difference. A randomized case–control trial of 100 patients with a variety of wounds compared the efficacy and outcomes of dressings saturated in superoxide solution (Group A) or in povidone-iodine (Group B) (14). The most common infecting organism isolated was P. aeruginosa, followed by Staphylococcus aureus and Klebsiella spp. The decrease in surface area of wounds at the end of 1, 2, 3 and 4 weeks, was statistically significantly greater in Group A than Group B ($P = 0.005$, $P = 0.002$, $P < 0.001$ and $P = 0.001$, respectively). A randomized controlled trial examined the efficacy and safety of a super-oxidized solution compared with povidone-iodine (as adjuncts to systemic antibiotics and debridement as needed) in the management of wide (> 5 cm) post-surgical lesions of the diabetic foot in 40 patients with post-surgical wounds (15). Healing, as measured by complete re-epithelization, occurred in 90% of the patients treated with super-oxidized solution compared with 55% in the povidone-iodine group ($P < 0.01$). The group treated with super-oxidized solution also had fewer episodes of reinfection ($P < 0.01$). In a retrospective analysis of a cohort of 897 patients with 1249 venous leg ulcers treated with hypochlorous acid solution, all the ulcers healed completely (16). Treatment involved cleaning and debriding foreign matter, debris and necrotic material via application of hypochlorous acid solution, with or without pressure and abrasion using hypochlorous acid-soaked sterile gauze. Sharp debridement was performed where required within 10 days of presentation. All ulcers were dressed and/or loosely packed with hypochlorous acid-soaked sterile gauze. Compressive bandaging was applied. Light abrasion using sterile gauze and flushing with hypochlorous acid solution were done every few days. Longest healing times were observed in 10 patients for whom compression therapy was contraindicated. However, aggressive management adding hypochlorous acid resulted in complete wound closure within 180 days for this treatment-refractory group (16). A randomized, single-blind trial studied the effect of standard of care with or without neutral pH super oxidized solution in the treatment of 45 patients with diabetic foot ulcers (17). Odour reduction was reported in 100% of patients treated with super-oxidized solution, compared with 20% in the standard care group. Surrounding cellulitis diminished in 80.5% versus 43.7% of patients and advancement to the granulating tissue stage in 90.4% versus 62.5% of patients were observed in the super-oxidized and standard care groups, respectively. One hundred patients with diabetic foot ulcer wounds were randomized to treatment with either daily super-oxidized water (hypochlorous acid) or saline-soaked gauzes (18). Patients treated with hypochlorous acid had a significantly

shorter period of hospitalization than saline-treated patients: 1–7 days hospitalization for 68% of patients treated with hypochlorous acid versus for 20% treated with saline-soaked gauzes; $P < 0.05$). A higher proportion in the hypochlorous acid group experienced a down-grading of their ulcers (62% versus 15%; $P < 0.05$). A study prospectively randomized 200 patients with different types of wounds to treatment with either gauze saturated in hypochlorous acid or in povidone-iodine and with antibiotics (19). After a mean follow-up of 21 days, the average reduction in the wound size of diabetic foot ulcer in the hypochlorous acid group was 70% compared with 50% in the povidone iodine group. Earlier granulation and epithelization were seen in the wounds treated with hypochlorous acid solution compared with those treated with povidone-iodine (100% versus 85% at day 18).

Torts

No new evidence for safety of hypochlorous acid solution was presented in the current application compared with the 2021 application. The following summary is reproduced from the technical report of the 2021 Expert Committee meeting (2). Clinical adverse events from exposure to pure hypochlorous acid (present at a pH between 4.0 and 5.33) have not been recorded in the medical literature. However, reports of incidents following exposure to relatively high pH, crude formulations (> 6.5) containing mixed oxidants, including hypochlorite, have occurred due to poorly controlled manufacturing processes. 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 or in swimming pools that are improperly managed and allow pH to rise into the alkaline range. A 2011 study evaluated the risk of biological toxicity in a mouse model when hypochlorous acid was ingested as drinking water for 8 weeks. Hypochlorous acid had no systemic effects in that animal model and the authors concluded it would be safe if used as a mouthwash, even if ingested (20). Another study using an animal model looked at the potential toxicity of infusions of hypochlorous acid into the intraperitoneal cavity of rats. No statistical difference in blood biochemistry, renal function or liver function was found in rats infused with hypochlorous acid (21). A review of hypochlorous acid versus normal saline as a peritoneal lavage to prevent post-surgical infections after perforated appendicitis in children found no evidence of toxicity associated with hypochlorous acid (22). Environmental safety Hypochlorous acid is a highly reactive molecule and short-lived when exposed to pathogens or another bioload. On exposure, pure hypochlorous acid degrades within minutes to sodium chloride and water, becoming benign and non-reactive saltwater closely analogous to human tears (23). Because of that rapid reactivity, pure hypochlorous acid at a label concentration of 180 ppm poses no risk of environmental contamination (except as a mild 0.9% salt solution) and does not require personal protective equipment, can be stored with no hazardous materials protocol and can be disposed of with no risk of generating a toxic waste stream. In contrast, impure hypochlorous acid/hypochlorite solutions, such as hypochlorite (bleach), require personal protective equipment and hazardous material storage, and must be disposed of as both a toxic materials risk and an environmental hazard. Those same hazard considerations also apply to other classes of antisepsis and disinfection agents.

Rapport coût/efficacité

No cost–effectiveness data were presented in the application. The application stated that current product pricing at scale can probably be achieved at less than 1 euro per wholesale litre, with minor regional variations based on water, salt and energy costs.

Directives de l'OMS

WHO interim guidance on cleaning and disinfection of environmental surfaces in the context of COVID-19 (24) states that the selection of disinfectants should take into account: the microorganisms targeted; the recommended concentration and contact time; compatibility of chemical disinfectants and surfaces being disinfected; toxicity; ease of use; and product stability. Hypochlorite-based products include liquid (sodium hypochlorite), solid or powdered (calcium hypochlorite) formulations. These formulations dissolve in water to create a dilute aqueous chlorine solution in which undissociated hypochlorous acid is active as the antimicrobial compound.

Disponibilité

The application stated that production of hypochlorous acid in local manufacturing facilities is routine and has the advantage of eliminating the cost of transport. Proprietary products are also available.

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Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; https://apps.who.int/iris/handle/10665/259481). License: CC BY-NC-SA 3.0 IGO.
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