



## Otic Anti-Infectives and Anesthetics Therapeutic Class Review (TCR)

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February 1, 2015

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## FDA-APPROVED INDICATIONS<sup>1,2</sup>

Drug Name	Manufacturer	Indication(s)
acetic acid	generic	For the treatment of otitis externa
acetic acid / hydrocortisone (Acetasol HC)	generic	For the treatment of otitis externa
acetic acid in aluminum acetate	generic	For the treatment of otitis externa

## OVERVIEW

The standard treatment for acute otitis media (AOM) is the use of systemic antibiotics while topical (otic) therapy antibiotic is recommended for uncomplicated otitis externa.

Acute otitis externa (AOE) is an acute inflammation of the external auditory canal. Commonly referred to as “swimmer’s ear” or “tropical ear,” this condition is often precipitated by water exposure or trauma. The etiology is typically bacterial; the most common pathogens implicated are *Pseudomonas aeruginosa* and *Staphylococcus aureus*, often occurring as a polymicrobial infection. Patients will typically complain of otalgia and otorrhea, and the ear canal may appear erythematous and swollen. It is imperative that the ear canal be cleared of any discharge or debris that can occlude the canal since the presence of such material can keep the canal moist and interfere with topical treatment. All ages are affected, with a peak incidence in children aged 7 to 12 years.

In 2014, the American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) released updated guidelines for the management of AOE in patients over two years of age.<sup>3</sup> They recommend the use of topical preparations for initial therapy of diffuse, uncomplicated AOE. Systemic antimicrobial therapy should not be used unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy (e.g., diabetes, immune deficiency, non-intact tympanic membrane, presence of tympanostomy tubes). Management of AOE should include an assessment of pain and analgesic treatment prescribed based on pain severity. Effective topical treatments include otic antibiotics (e.g., aminoglycosides, polymyxin B, quinolones), otic steroids (e.g., hydrocortisone), and low pH antiseptics (e.g., aluminum acetate or acetic acid).<sup>4</sup>

Evidence supports equivalent results with ear cleansing, an ear wick, and any of the choices of topical agents, including acidifying agents, antibiotics, antibiotic and steroid combinations, or antifungal agents.<sup>5</sup> The choice of therapy should be based on efficacy, low incidence of adverse events, patient preferences, and the likelihood of adherence to therapy. Factors related to patient preference include adverse effects, drug costs, frequency and duration of treatment, and analgesic choice based on pain tolerance.<sup>6</sup>

Many agents previously within this class had been marketed prior to the Food and Drug Administration (FDA) requirement that all drugs must be proven safe and effective (drugs entering the market between 1938 and 1962); thus, they were not considered FDA-approved but were commercially available for dispensing and use.<sup>7</sup> The Federal Food, Drug, and Cosmetic Act of 1962 allowed for the Drug Efficacy Study Implementation (DESI) review program, which provided a method for these agents to receive retrospective approval, but would also allow these agents to remain on the market in the meantime. In 2006, the FDA began an initiative to remove these unapproved but available products,

sometimes referred to as DESI drugs, from the market if they did not meet the safety and efficacy requirement for approval.

In July 2015, the FDA removed multiple otic preparations previously in this class.<sup>8</sup> Agents containing the following active ingredients are considered to be unapproved drug products: benzocaine; benzocaine and antipyrine; benzocaine, antipyrine, and zinc acetate; benzocaine, chloroxylenol, and hydrocortisone; chloroxylenol and pramoxine; and chloroxylenol, pramoxine, and hydrocortisone. As a result, these agents are no longer included in this review.

## PHARMACOLOGY<sup>9,10</sup>

Acetic acid is a low pH antiseptic agent. Its mechanism of action is unknown.

Hydrocortisone is a corticosteroid that controls inflammation, edema, pruritus, and other dermal reactions.

## PHARMACOKINETICS<sup>11</sup>

Due to the topical application of these products, minimal systemic absorption is expected.

## CONTRAINDICATIONS/WARNINGS<sup>12,13</sup>

All products in this review are contraindicated in people with hypersensitivity to any of the ingredients contained in the product, and in persons with perforated tympanic membrane or unexplained discharge from the ear.

These agents should be discontinued if sensitization or irritation occurs.

These agents are for otic use only. Avoid accidental exposure to the eyes.

## DRUG INTERACTIONS<sup>14</sup>

No clinically relevant drug-drug interactions are expected with agents in this review when used as an otic agent.

## ADVERSE EFFECTS<sup>15,16</sup>

The products in this review are generally tolerated well; however, stinging, burning local irritation, contact dermatitis, or hypersensitivity reactions can occur.

Discontinue treatment if signs and symptoms (e.g., burning, pruritus, redness, or oozing sores in ear) of a local allergic reaction occur.

Warming an otic product by holding the bottle in hand for 1 to 2 minutes may minimize dizziness and pain on application; do not heat above body temperature.

## SPECIAL POPULATIONS<sup>17,18</sup>

### Pediatrics

Children may absorb proportionally larger amounts of topical corticosteroids, such as hydrocortisone (Acetasol HC), and, therefore, may be more susceptible to systemic toxicity, such as HPA axis suppression and Cushing's syndrome. Pediatric patients should be given the least amount needed for an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Safety and effectiveness of acetic acid containing products in pediatric patients below the age of 3 years have not been established.

### Pregnancy

All agents in this review are classified as Pregnancy Category C.

## DOSAGE AND ADMINISTRATION<sup>19,20</sup>

Drug	Indication/Dosages	Package size
acetic acid	Instill 4 to 6 drops into ear canal(s). Repeat every 2 to 3 hours.	2% - 15 mL
acetic acid / hydrocortisone (Acetasol HC)	Insert a cotton wick into the ear canal and saturate with medication. Keep wick moist by adding 3 to 5 drops every 4 to 6 hours. May remove the wick after 24 hours and continue to instill 3 to 5 drops into the ear canal(s) 3 to 4 times per day. The lower end of the dosage range is usually recommended in children.	2% /1% - 10 mL
acetic acid in aluminum acetate	Instill 4 to 6 drops into the ear canal(s). Repeat every 2 to 3 hours.	2% - 60 mL

Patients should be instructed to remain still while medication is in the ear canal for 3 to 5 minutes.<sup>21</sup>

If obstruction in the ear canal is evident, aural cleansing (aural toilet) to remove obstructing debris and placement of a wick, if edema prevents drug delivery, should be considered.<sup>22</sup>

In general, it is recommended that drops be given for 3 days beyond the cessation of symptoms (typically 5 to 7 days); however, in patients with more severe infections, 10 to 14 days of treatment may be required.<sup>23</sup>

## CLINICAL TRIALS

### Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. *Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation.* Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies eligible for inclusion in this therapeutic class review were evaluated for results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, eligible studies have also been evaluated for validity and importance. There are no published comparative studies meeting these criteria.

### SUMMARY

The products in this review contain combinations of antiseptic and anti-inflammatory compounds and are used topically for the treatment of otitis externa.

The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) recommends topical preparations for initial therapy of uncomplicated acute otitis externa, while systemic antimicrobial therapy should be used if there is extension outside the ear canal, or if specific host factors are present.

Similar results have been reported with any of the choices of topical agents, including antibiotics and antibiotic and steroid combinations, in the treatment of otitis externa.

All products in this review are contraindicated in persons with perforated tympanic membranes or unexplained discharge from the ear.

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