

A. Nasal Moisturizer Drug Products

The agency considers nasal moisturizer products³ to be drugs when they contain the following or similar ingredients: Sodium chloride, normal saline, buffered isotonic saline solution, saline phosphate buffer solution, glycerin. A number of these nasal moisturizer products have been marketed for several years with various labeling claims. Such claims include the following statements:

- “provides soothing moisture to dry, inflamed nasal membranes due to colds, allergies, low humidity, and other minor nasal irritations”

- “restores vital moisture to provide prompt relief for dry, crusted, and inflamed nasal membranes due to chronic sinusitis, colds, low humidity, overuse of nasal decongestant drops and sprays, allergies, minor nose bleeds, and other minor nasal irritations”

- “use for dry nasal membranes caused by chronic sinusitis, allergy, asthma, dry air, oxygen therapy”

- “rhinitis medicamentosa, rhinitis sicca, and atrophic rhinitis for patients ‘hooked on nose drops’ and glaucoma patients on diuretics having dry nasal capillaries”

- “a nasal moisturizer formulated to be physiologically compatible with nasal membranes, providing soothing relief for clogged nasal passages without stinging or burning”

- “restores moisture to relieve dry, inflamed nasal membranes due to low humidity, colds, allergies, and overuse of nasal decongestants”.

FDA currently desires additional data on which to make a determination as to the safety, effectiveness, and labeling of these products. There may be other labeling statements or formulations of the products that are marketed as OTC nasal moisturizers. FDA considers many of these claims to be drug claims and believes these products should be regulated under the monograph for OTC cough-cold or miscellaneous internal drug products. Therefore, FDA requests that interested persons who have data and information on the safety and effectiveness of nasal moisturizer products submit them to FDA at this time.

³In its report on OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the *Federal Register* of September 9, 1976 (41 FR 38312)), the panel that reviewed these products classified saline phosphate buffer solution as an inactive ingredient or pharmaceutical necessity, and did not classify it as a nasal moisturizer. The panel did not review and evaluate products used as nasal moisturizers, and these products were not reviewed and evaluated in the various tentative final and final monographs under the rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products.

B. Urinary Analgesic/Antiseptic Drug Products

FDA is also aware that products marketed as urinary analgesics/antiseptics and products for too frequent, burning, and painful urination have been marketed for a number of years, but have not yet been evaluated as part of the OTC drug review.⁴ Other products marketed for these uses for a number of years contain methylene blue and phenazopyridine hydrochloride (HCl).

Phenazopyridine HCl has had a dual prescription/OTC marketing status based on the ingredient's extensive marketing history in the United States that predates the 1951 Durham-Humphrey Amendments to the Federal Food, Drug, and Cosmetic Act (the act). FDA reviewed phenazopyridine HCl/sulfonamide combination products under the Drug Efficacy Study Implementation (DESI 12056) for the treatment of urinary tract infections caused by a sulfonamide-susceptible organism when relief of symptoms of pain, burning, or urgency is needed. None of the single-entity phenazopyridine HCl drugs marketed at that time or now have been the subject of an approved new drug application (NDA).

In the *Federal Register* of July 29, 1983 (48 FR 34516), FDA published a DESI notice containing conditions for approval and marketing of phenazopyridine-containing drug products (single entities or fixed combinations). The notice announced certain required labeling statements for phenazopyridine-containing drug products indicated for use in relieving symptoms associated with a urinary tract infection, and certain required labeling for all phenazopyridine-containing drug products. FDA recommended the following labeling requirements for phenazopyridine-containing drug products (single entities or fixed combinations) for use in the treatment of urinary tract infections:

1. The following information shall be disclosed in the INDICATION section (adapted to the labeling of particular drug products): Treatment of a urinary tract infection with phenazopyridine HCl or a combination drug product containing phenazopyridine HCl should not exceed 2 days because there is lack of evidence that the combined administration of phenazopyridine HCl

⁴A product containing methenamine, sodium salicylate, salicylamide, and benzoic acid was submitted in response to the 1973 and 1975 call-for-data notices mentioned previously, but has not been reviewed to date. This submission is out-of-date and needs to be updated before the agency begins its review of these products.

and an antibacterial provides greater benefit than administration of the antibacterial alone after 2 days.

2. The part of the INDICATION section pertaining to the use of the product in urinary tract infections shall also refer to the DOSAGE and ADMINISTRATION section.

3. In its dosage and dosing interval recommendations pertaining to the use of the product in urinary tract infections, the DOSAGE and ADMINISTRATION section shall show that the product is only indicated for up to 2 days (the effect of phenazopyridine HCl should not be relied upon after 48 hours).

The DESI notice also contained the following labeling requirement for all drug products containing phenazopyridine:

The following statement shall be included in the CARCINOGENESIS subsection of the PRECAUTION section of the labeling:

Long-term administration of phenazopyridine hydrochloride has induced neoplasia in rats (large intestine) and mice (liver). Although no association between phenazopyridine hydrochloride and human neoplasia has been reported, adequate epidemiological studies along these lines have not been conducted.

This information came from a National Cancer Institute technical report (Ref. 1). FDA is not aware of any epidemiological studies that have been done since the report was published in 1978.

The 1983 DESI notice states that the product considered (Azo Gantanol) contained 500 milligrams (mg) of sulfamethoxazole (antibacterial component) and 100 mg of phenazopyridine HCl (analgesic component) per tablet, and this combination is effective only for the first 48-hour treatment period (four tablets initially followed by two tablets every 12 hours, with the last dose administered at 36 hours). There is no evidence that the phenazopyridine HCl component has a beneficial effect on symptoms beyond 48 hours. Therefore, after initial treatment with the combination product, further treatment should be continued only with the sulfonamide.

The way the labeling information appeared in the notice indicated that 200 mg of phenazopyridine was the prescription dose. Products containing lesser amounts (e.g., 190 or 195 mg) have been marketed OTC. The recommended dosage is three times a day after meals. OTC drug products containing phenazopyridine HCl as a urinary analgesic are usually labeled: “Can be used up to 3 times daily for 2 days maximum.” One product surveyed (Ref. 2) does not contain the required