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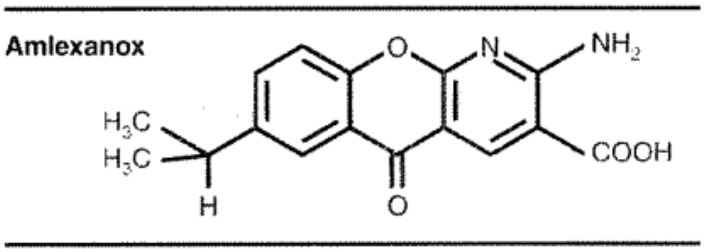
Aphthasol®

(amlexanox oral paste),

For Oral Cavity Use Only
Not for Ophthalmic Use

Description: Aphthasol contains 5% amlexanox in an adhesive oral paste. Chemically, amlexanox is 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano[2,3-b] pyridine-3-carboxylic acid. It has a molecular formula of $C_{16}H_{14}N_2O_4$ and has a molecular weight of 298.30. Amlexanox is odorless, white to yellowish-white crystalline powder. The structural formula is:



Each gram of beige colored oral paste contains 50 mg of amlexanox in an adhesive oral paste base consisting of benzyl alcohol, gelatin, glyceryl monostearate, mineral oil, pectin, petrolatum, and sodium carboxymethylcellulose.

Clinical Pharmacology: The mechanism of action by which amlexanox accelerates healing of aphthous ulcers is unknown. *In vitro* studies have demonstrated amlexanox to be a potent inhibitor of the formation and/or release of inflammatory mediators (histamine and leukotrienes) from mast cells, neutrophils and mononuclear cells. Given orally to animals, amlexanox has demonstrated anti-allergic and anti-inflammatory activities and has been shown to suppress both immediate and delayed type hypersensitivity reactions. The relevance of these activities of amlexanox to its effects on aphthous ulcers has not been established.

Pharmacokinetics and Metabolism: After a single oral application of 100 mg of paste (5 mg amlexanox), maximal serum levels of approximately 120 ng/ml are observed at 2.4 hours. Most of the systemic absorption of amlexanox is via the gastrointestinal tract, and the amount absorbed directly through the active ulcer is not a significant portion of the applied dose. The half-life for elimination was 3.5 +/- 1.1 hours in healthy individuals. Approximately 17% of the dose is eliminated into the urine as unchanged amlexanox, a hydroxylated metabolite, and their conjugates. With multiple applications four times daily, steady state levels were reached within one week, and no accumulation was observed with up to four weeks of usage.

Clinical Studies: The safety of amlexanox oral paste, 5%, was established in a study in which 100 patients with aphthous ulcers applied the medication four times daily for 28 days with no significant topical or systemic adverse effects. The effectiveness was demonstrated in three controlled clinical studies of patients with mild to moderate aphthous ulcers which evaluated 464 patients receiving amlexanox oral paste, 5%, 465 patients receiving a placebo paste, and 195 patients receiving no treatment. Amlexanox oral paste, 5%, was shown to accelerate healing of aphthous ulcers in a statistically significant manner as compared to both vehicle and no

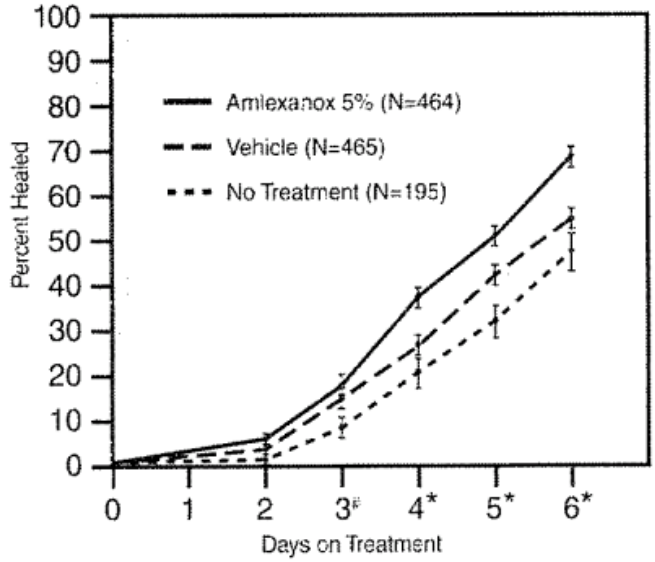
treatment.

Amlexanox oral paste, 5%, versus no treatment: In the combined database of the two studies including a no treatment group, there was a significant difference in the rate of ulcer healing which translated to a reduction of 1.6 days in the median time to complete healing and a reduction of 1.3 days in the median time to complete pain relief. After 3 days of treatment there was a significant difference in both percent of patients with complete healing of ulcers (21% vs. 8%) and percent of patients with complete resolution of pain (44% vs. 20%).

Amlexanox oral paste, 5%, versus vehicle: In the combined database of the three studies, there was a significant difference in the rate of ulcer healing which translated into a reduction of 0.7 days in the median time to complete healing, and a reduction of 0.7 days in the median time to complete pain relief. After 4 days of treatment there was a significant difference in both percent of patients with complete healing of ulcers (37% vs. 27%) and percent of patients with complete resolution of pain (60% vs. 49%).

Pain relief occurred in conjunction with healing of the ulcers. Amlexanox oral paste, 5%, by itself, was not shown to be an analgesic medication. The safety and effectiveness of the product in immunocompromised individuals has not been assessed.

Cumulative % of Patients with Healed Ulcers



Results for amlexanox, 5%, vs. vehicle are based on three clinical trials. Results for amlexanox, 5%, vs. no treatment are based on two clinical trials.
* denotes statistically significant superiority of amlexanox, 5%, vs. vehicle and no treatment.
# denotes statistically significant superiority of amlexanox, 5%, vs. no treatment.
Error bars represent Standard Error of the Mean.

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Indications and Usage: Amlexanox oral paste, 5%, is indicated for the treatment of aphthous ulcers in people with normal immune systems.

Contraindications: Amlexanox oral paste, 5%, is contraindicated in patients with known hypersensitivity to amlexanox or other ingredients in the formulation.

Precautions:

General: Wash hands immediately after applying amlexanox oral paste, 5%, directly to ulcers with the finger tips. In the event that a rash or contact mucositis occurs, discontinue use.

Information for Patients:

1. Apply the paste as soon as possible after noticing the symptoms of an aphthous ulcer. Continue to use the paste four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and at bedtime.

2. Dry the ulcer(s) by gently patting it with a soft, clean cloth.

3. Wash your hands before applying the Aphthasol.

4. Moisten the tip of your index finger.

5. Squeeze a dab of paste approximately 1/4 inch (0.5 cm) onto a finger tip.

6. Gently dab the Aphthasol on to the ulcer. Repeat the process if you have more than one ulcer.

7. Wash your hands when you are done applying Aphthasol.

8. Wash eyes promptly if they should come in contact with the paste.

9. Use the paste until the ulcer heals. If significant healing or pain relief has not occurred in 10 days, consult your dentist or physician.

10. Keep out of the reach of children.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Amlexanox was not carcinogenic when administered orally to rats for two years and to mice for 18 months. *In vitro* (Ames) and *in vivo* (mouse micronucleus) mutagenicity tests of amlexanox were negative. Amlexanox at doses up to two hundred times the projected human daily dose, on a mg/m^2 basis, did not significantly affect fertility or general reproductive performance in rats.

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Pregnancy Category B: Teratology studies were performed with rats and rabbits at doses up to two hundred and six hundred times, respectively, the projected human daily dose, on a mg/m^2 basis. No adverse fetal effects were observed. At doses up to two hundred times the projected human daily dose, on a mg/m^2 basis, amlexanox did not have significant effect on peri- and postnatal development of rat fetuses. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Amlexanox was found in the milk of lactating rats; therefore, caution should be exercised when administering amlexanox oral paste, 5%, to a nursing woman.

Pediatric Use: Safety and effectiveness of amlexanox oral paste, 5%, in pediatric patients have not been established.

Geriatric Use: Clinical studies of Aphthasol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Adverse Reactions: Adverse reactions considered related or possibly related to amlexanox oral paste, 5%, were not reported by more than 5% of patients. Adverse reactions reported by 1-2% of patients were transient pain, stinging and/or burning at the site of application. Infrequent (< 1%) adverse reactions in the clinical studies were contact mucositis, nausea, and diarrhea.

Overdosage: There are no reports of human ingestion overdosage. Ingestion of a full tube of 5 grams of paste would result in systemic exposure well below the maximum nontoxic dose of amlexanox in animals. Gastrointestinal upset such as diarrhea and vomiting could result from an overdose.

Dosage and Administration: The paste should be applied as soon as possible after noticing the symptoms of an aphthous ulcer and should be used four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and at bedtime. Squeeze a dab of paste approximately 1/4 inch (0.5 cm) onto a finger tip. With gentle pressure, dab the paste onto each ulcer in the mouth. Use of the medication should be continued until the ulcer heals. If significant healing or pain reduction has not occurred in 10 days, consult your dentist or physician.

How Supplied: Amlexanox oral paste, 5%, is supplied in 5 gram tubes (NDC10158-059-01). Amlexanox oral paste, 5%, should be stored at controlled room temperature, 15°-30°C (59°-86°F).

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Manufactured for:

Oral Health Care Division
Block Drug Company, Inc.
Jersey City, NJ 07302

By Reedco, Inc.
Humacao, Puerto Rico 00791

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Block Drug Company, Inc.

June 2002 APH-PI-0l

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/s/

Markham Luke
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Acting for Dr. Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products