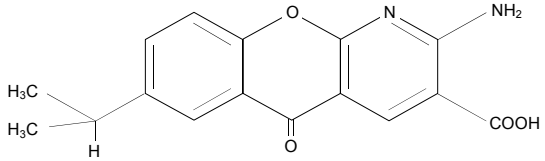
TRADENAME
(amlexanox) Mucoadhesive Patch, 2 mg
For Oral Cavity Use Only

Description: TRADENAME is a mucoadhesive patch that contains 2 mg of amlexanox per patch.

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 an odorless, white to yellowish-white crystalline powder. The structural formula is:



Each patch contains 2 mg of amlexanox as part of a multi-layer patch consisting of ethylcellulose, FD&C Blue #1, FD&C Red #40, hydroxyethylcellulose, hypromellose, methylparaben, modified starch, polycarbophil, povidone, propylene glycol, propylene glycol monostearate, purified water, sodium benzoate, 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.

Pharmacokinetics and Metabolism: After oral application of TRADENAME patches, the average maximum serum levels are 45.4 ng/ml (N=14), and 168 ng/ml (N=3) after application of one or three patches, respectively. The mean total exposure, AUC_{0-24}, is 258 ng•hr/ml, and 605 ng•hr/ml after application of one, or three patches, respectively.

After 3 full days of oral application of TRADENAME, four times a day, and one dose on Day 4, maximum serum levels ranged from BLQ (Below limit of quantification: 5 ng/mL in serum) to 79 ng/ml (N=24) prior to the first dose on Day 4, and also, had a similar range in the serum samples collected 2 hours post-dose. For application of two TRADENAME patches, the pre- and post-dose levels were BLQ to 164 ng/mL and BLQ to 117 ng/mL, (N=5) respectively. Post-dose levels are similar to or slightly higher than pre-dose levels, with the mean level of 9.8 and 16 ng/mL, respectively, for one TRADENAME patch and 44 and 44 ng/mL, respectively, for two TRADENAME patches.

CLINCIAL STUDIES

Study A

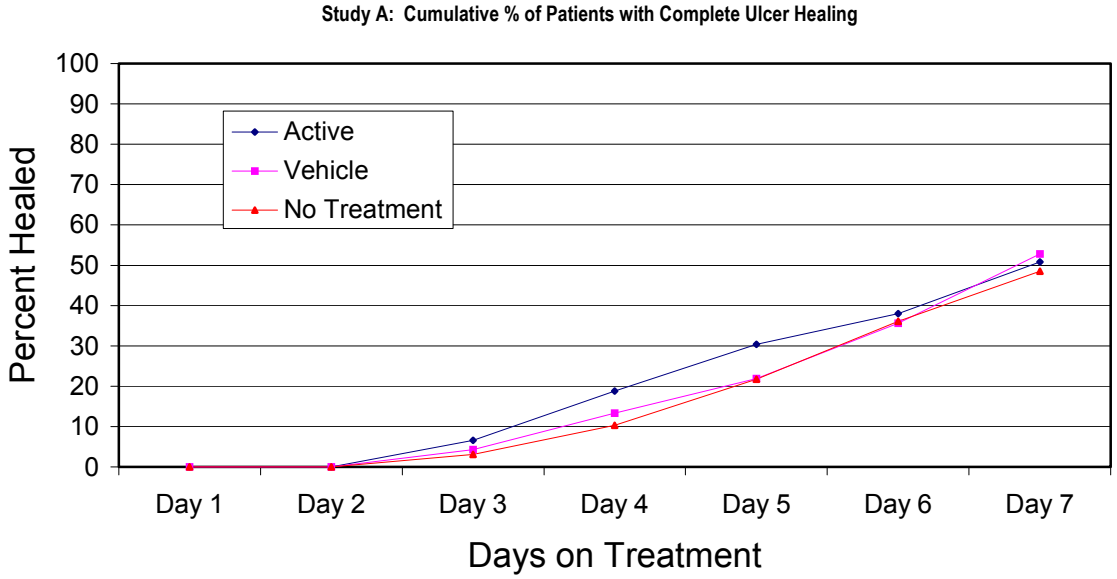
The efficacy of TRADENAME was established in one controlled clinical study, Study A, in which patients with one, two or three aphthous ulcers applied the patch(s) four times daily for 7 days. The study evaluated 303 patients receiving TRADENAME, 301 patients receiving the vehicle patch, and 97 patients receiving no treatment. Tobacco users and diabetics were excluded from clinical testing.

The endpoint agreed upon *a priori* was complete healing on Day 5. After 4 days of treatment (Day 5) there was a significant difference in percentage of patients with complete healing of ulcers (30.4% in the active group vs. 21.9% in the vehicle group). In the following table, the percentage of patients healed in each group at each day of the study is provided.

Number (%) of Patients with Complete Ulcer Healing Over Time – Study A

Time	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
Day 4	57 (18.8%)	40 (13.3%)	10 (10.3%)
Day 5*	92 (30.4%)	66 (21.9%)	21 (21.6%)
Day 6	115 (38.0%)	107 (35.6%)	35 (36.1%)
Day 7	154 (50.8%)	159 (52.8%)	47 (48.5%)
* The comparison (p-value) of amlexanox vs. vehicle is statistically significant ($p<0.05$) at Day 5 only.			

The data from the above table is provided graphically as follows:



Pain relief occurred in conjunction with healing of the ulcers. TRADENAME, by itself was not shown to be an analgesic medication.

Indications and Usage: TRADENAME is indicated for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older. TRADENAME is not indicated for use in children below age 12 or in patients with an abnormal immune system.

Contraindications: TRADENAME, is contra-indicated in patients with known hypersensitivity to amlexanox or other ingredients in the formulation.

Precautions:
<u>General</u>

Wash hands immediately after applying TRADENAME directly to the ulcers with the fingertips. In the event that a rash or contact dermatitis occurs, discontinue use.

Use of TRADENAME in Smokers
Tobacco users may respond differently to TRADENAME. Smokers are known to have a lower incidence of aphthous ulcers than the general population, but were excluded from the clinical trials. Therefore, the effect of TRADENAME on smokers is not known.

Risk of Aspiration

There were no reports of accidental aspiration or detrimental swallowing of the patches in patients 12 and older during clinical trials. Nevertheless, it is recommended to apply TRADENAME at least 80 minutes prior to bedtime to avoid the possibility of aspiration of soft food-like particles that may come loose during erosion of the patch in the mouth. Keep out of the reach of children below the age of 12.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Amlexanox was not carcinogenic when administered to mice for 18 months at dosages up to 100 mg/kg/day (approximately 12 times the maximum human dose when comparing on the basis of body surface area estimates) or to rats for 24 months at dosages up to 250 mg/kg/day (approximately 60 times the maximum human dose). Amlexanox was negative in bacterial mutation assays in Salmonella, E. coli, and B. subtilis, in a mouse lymphoma assay, and in a micronucleus assay conducted in mice.

Amlexanox did not affect reproductive performance (fertility) or ability of rats to deliver and rear pups (perinatal development) when administered at dosages up to 300 mg/kg/day (approximately 70 times the maximum human dose).

Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates) and have revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, 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 in administering TRADENAME to a nursing woman.

Pediatric Use: The safety of TRADENAME in pediatric patients between ages 12 and 17 was established in a study in which patients with aphthous ulcers (98 of whom were pediatric) applied the patch four times daily for 7 days with no significant topical or systemic adverse effects. In a separate, long-term study 106 patients with aphthous ulcers (30 of whom were pediatric) applied the patch four times daily for 28 days with no significant topical or systemic adverse effects. Use of TRADENAME in patients under 12 is not recommended due to the risk of aspiration.

Geriatric Use: Safety and effectiveness of TRADENAME in geriatric patients have not been established.

Adverse Reactions: In the combined safety database, no single adverse reaction was reported by more than 10% of patients. Adverse reactions reported by 9.8% of patients were pain or burning,

restricted to the site of application, occurring at the time of application. Adverse reactions reported by less than 2% of patients were irritation and paresthesia at the site of application.

Systemic adverse events that occurred during clinical trials, that were reported by less than 2% of patients, included headache, sore throat, and nausea. Mouth ulceration (new aphthous ulcers) was also reported at a rate of less than 2%.

The safety of TRADENAME was established in a long-term study in which 106 patients with aphthous ulcers applied the patch four times daily for 28 days with no significant topical or systemic adverse effects.

The following table provides a comparison of the adverse events reported by patients in the clinical trials who received TRADENAME, a vehicle patch, and no treatment.

Percentage of Patients with Adverse Events with an Incidence of > 1% - from All Clinical Trials

	Amlexanox	Vehicle	No treatment
Application Site Reactions	N = 409	N = 301	N = 97
Pain	29 (7.1)	25 (8.3)	NA
Burning	11 (2.7)	9 (3.0)	NA
Irritation	6 (1.5)	6 (2.0)	NA
Reaction NOS	5 (1.2)	0 (0)	NA
Paresthesia	3 (0.7)	4 (1.3)	NA
Gastrointestinal Disorders			
Mouth Ulceration (i.e., new aphthous ulcers)	5 (1.2)	13 (4.3)	6 (6.2)
Nausea	4 (1.0)	5 (1.7)	0
Sore Throat NOS	1 (0.2)	3 (1.0)	1 (1.0)
Investigations			
Liver function tests NOS abnormal	2 (2.0)	Not done	Not done
Nervous System Disorders			
Headache NOS	6 (1.5)	4 (1.3)	0

Overdosage: There are no clinical reports of overdosage. Gastrointestinal upset such as nausea, vomiting, and diarrhea could result from an overdose.

Dosage and Administration: TRADENAME 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 80 minutes before bedtime. Up to three patches may be used at one time. Apply one TRADENAME patch to each ulcer. Use of the medication should be continued until the ulcer heals but no longer than 10 days. If significant healing or pain reduction has not occurred in 10 days, consult your dentist or physician.

Information for Patients:

1. Apply TRADENAME as soon as possible after noticing the symptoms of an aphthous ulcer. Wash hands before applying TRADENAME. Continue to use TRADENAME four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and 80 minutes before bedtime. In all cases, ensure that the patch is firmly attached to the ulcer.

2. In case of multiple ulcers, apply one TRADENAME patch to each ulcer. Up to 3 patches may be used at one time.
3. Using clean dry hands, place the light colored side of the patch against the ulcer in the mouth and press gently. The patch will stick to the ulcer in the mouth and remain in place. In rare circumstances, patients may find that the patch does not adhere readily. In such cases reapply the patch and press gently for several seconds before removing the finger.
4. Wash hands immediately after applying TRADENAME.
5. Patients should not apply a patch within 80 minutes before bedtime, to ensure it has eroded before sleep.
6. Patients should avoid eating or drinking for an hour after applying the patch.
7. Following application, the patch will slowly erode in the mouth, generally disappearing entirely in 20-80 minutes. Depending on the location of the patch in the mouth, and factors such as the amount of saliva flow and mechanical action of the mouth, complete disappearance of the patch may take more or less time. Patients may feel small particles in the mouth as the patch erodes. These particles may safely be swallowed.
8. Use TRADENAME until the ulcer heals. If significant healing and pain reduction has not occurred in 10 days, consult your dentist or physician.
9. Keep out of the reach of children below age 12.

How Supplied: TRADENAME is supplied in bottles of 20 patches. NDC 67404-300-20

TRADENAME should be stored at 25 ^{0}C (77 ^{0}F)
[Caution: Avoid prolonged exposure to temperatures above 30^{0}C (86 ^{0} F)

RX ONLY

Manufactured for:
Access Pharmaceuticals, Inc.
Dallas, TX 75207

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