

Amlexanox for the Prevention and Treatment of Aphthous Ulcers

ORAL PASTE 5%

ORADISC™ 2 MG

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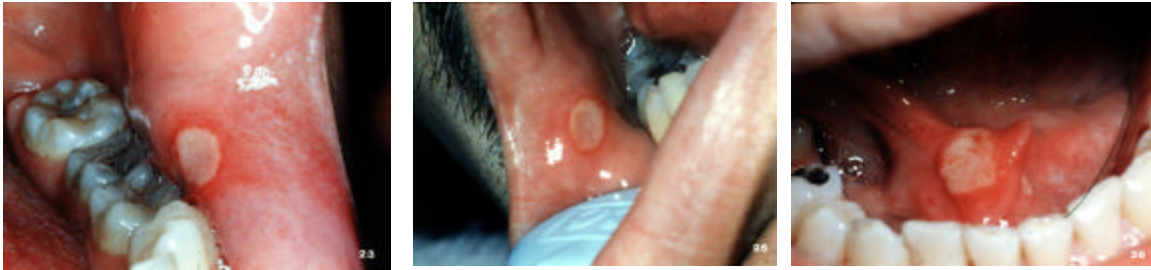


ACCESS
PHARMACEUTICALS, INC.

TABLE OF CONTENTS

<i>Recurrent Aphthous Ulcers (RAU) - The Disease</i>	<i>1</i>
<i>Treatment and Incidence Literature</i>	<i>2</i>
<i>Disease Statistics - Patient Research from Phase III Studies</i>	<i>3</i>
<i>Aphthous Ulcers - Key Market Research Findings</i>	<i>4</i>
<i>Amlexanox Pharmacology</i>	<i>5</i>
<i>Amlexanox Toxicology</i>	<i>6</i>
<i>Amlexanox 5% Paste - Clinical Data Summary</i>	<i>7</i>
<i>Amlexanox 5% Paste - Efficacy Summary</i>	<i>8</i>
<i>Amlexanox 5% Paste - Comparison of Clinical Data</i>	<i>9</i>
<i>Amlexanox 5% Paste - Product Summary</i>	<i>10</i>
<i>Amlexanox New Product Development - OraDiscTM</i>	<i>11</i>
<i>OraDiscTM - Product Development Status</i>	<i>12</i>

APHTHOUS ULCERS - THE DISEASE



Recurrent aphthous ulcers (RAU) or stomatitis (RAS) is characterized by painful, recurring ulcerations of the oral mucosa. It is the most common oral ulcerative disease in human beings yet a principal etiology has yet to be discovered. There is a significant body of evidence suggesting an immunologic mechanism as a cause of RAU. Recurrence may be precipitated by trauma, hormonal changes, physical or psychic stress and chemical irritants. Allergy and genetic factors have been associated with the disease. Of those factors which can potentially exacerbate RAU, several studies seem to support the association of minor mucosal trauma with ulcer onset in susceptible individuals. While the specific nature of the disease remains unknown, current evidence suggests aphthous stomatitis is a noninfectious inflammatory mucosal disease. Recurrences can last anywhere from 4 to 30 days, with most episodes lasting 7 to 10 days.

RAU is classified into three categories;

1. Minor aphthous Ulcers (80% -85% of RAU cases) are 1 – 10mm in diameter and heal in 7 - 10 days.
2. Major aphthous ulcers (Sutton disease) constitute 10% - 15% of RAU cases. These lesions are greater than 10mm and take 10-30 days or more to heal.
3. Herpetiform ulcers (5% – 10% of RAU) are multiple, clustered 1 to 3 mm lesions that may coalesce into plaques and generally heal in 7 – 10 days.

Minor aphthous ulcers are small, recurrent, moderately painful ulcers, with most episodes consisting of single ulcers. However, as many as 5 to 50 ulcers per episode have been observed in some patients with Herpetiform ulceration. In the prodromal stage, symptoms noticed by the patient may include a burning sensation or small swelling. At this stage only erythema (redness) of the surrounding mucosa may be noted on examination. Within a day or so an ulcer covered with white exudate will develop through

breakdown of the epithelium. This ulcer continues to increase in size becoming increasingly painful until healing begins by re-epithelialization (cell migration) over the site. The size of ulcers vary from 2-3 mm to 1 cm in diameter.

While the actual incidence of RAU is unknown, reports have indicated the incidence to be between 2% and 50% of the general population with most estimate suggesting 20%. It has been observed with a frequency as high as 50% in selected groups such as medical and dental students. The disease is slightly more prevalent in females than males and also among those individuals with a family history of the disease. Most patients initially demonstrate symptoms between 10 and 19 years of age, however, many patients may present with symptoms in early childhood.

Prior to amlexanox 5% paste (Aphthasol[®]), available treatment was largely symptomatic, with patient management being either entirely empiric or based on clinicians' perception of the cause of the ulcers. Goals of treating aphthous ulcers include;

1. accelerating the healing of ulcers
2. pain relief
3. prevention of recurrences.

TREATMENT AND INCIDENCE LITERATURE

"The beneficial effect of 5% amlexanox paste to accelerate the healing of aphthous ulcers has been clearly and consistently demonstrated in the four similarly designed, vehicle-controlled, studies described in this article".

Source: Khandwala A., Van Inwegen R.G., Alfano M.C. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers. Oral Surg, Oral Med, Oral Pathol, Oral Radiol Endo. 1997; 83:222-30.

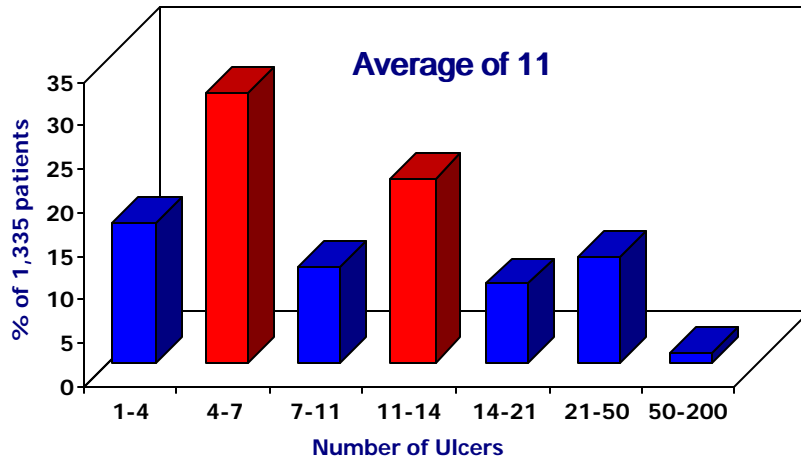
- *The most common oral mucosal disease known to human beings*
- *Prevalence of 20% in general population.*
- *As high as 50%to 60% in selected groups e.g. University students.*

Source: Ship JA - *Quintessence Int* - 01-Feb-2000; 31(2): 95-112

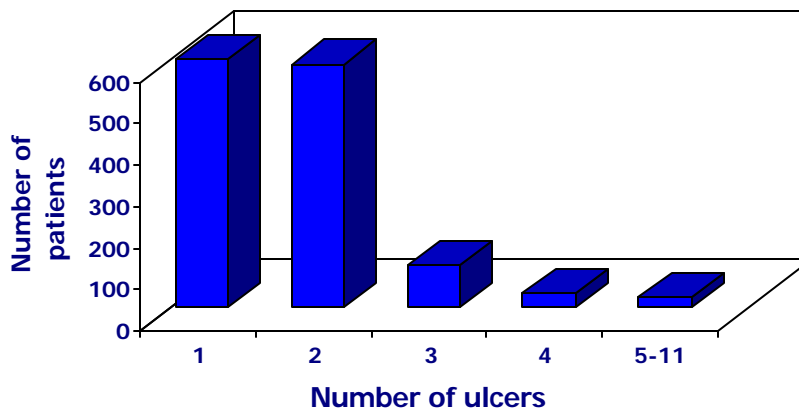
DISEASE STATISTICS FROM SURVEY OF PATIENTS IN PHASE III STUDIES

1,335 patients that participated in the Phase III Clinical trials for Amlexanox Paste 5% (Aphthasol®) were asked the following questions upon completing their participation in the clinical trial;

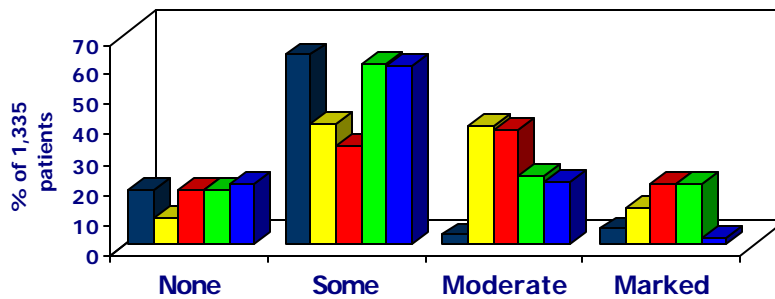
How Many Ulcer Episodes are Suffered Annually?



How Many Ulcers per Episode?



What is your Perception of the Benefit of your Current Products of Choice?



APHTHOUS ULCER MARKET RESEARCH

- ❑ Patients do not understand why they get aphthous ulcers. They are frustrating and interfere with basic quality of life issues such as eating, drinking and talking
- ❑ There is disappointment in the the lack of effective treatments
 - Most have tried a range of remedies including OTC products to a “magic mouthwash” made from various remedies giving at best temporary relief
- ❑ Product categories most often prescribed to treat aphthous ulcers:
 - Anesthetics 41%
 - Steroids 45%
 - Antibiotic/Antiviral/Antiseptic 19%
- ❑ Kenalog in Orabase is the most often prescribed product in the United States:
 - Currently 1.8 million prescriptions are written
- ❑ Reasons for dissatisfaction with currently prescribed products including Kenalog and Zilactin:
 - Products provide only temporary pain relief
 - Products do not cure
 - Products do not cover lesion
 - Cost
- ❑ New product benefits desired by physicians:
 - Accelerated healing time
 - Accelerated relief from pain
 - Reduced frequency of recurrence
 - Ease of patient use
- ❑ Based upon patient feedback Physicians and Dentists believe Amlexanox Paste 5% (Aphthasol) to be efficacious and convenient to use

- Patient feedback confirmed that Aphthasol reduces inflammation, reduced pain and healed the ulcers faster
- ❑ Patients having experience with Aphthasol stated the earlier the initiation of treatment the more effective the product is perceived.
 - A prodromal effect was recognized, several commented that if they applied Aphthasol just before an outbreak they could “nip” it in the bud in 24 hours
- ❑ Physicians as well as Dentists respond very positively to Aphthasol
 - Both agreed it was a problem in search of a solution
 - Interest was such that most recalled how they learned of Aphthasol
 - Compared to other treatments Aphthasol is seen as more effective and much easier for patients to use
 - Many prescribers suggest several alternatives advising patients that none are all that effective.
 - Having a single effective remedy was seen as clearly easier and better for the patient.
 - “Cocktail” mouthwash remedies requiring multiple prescriptions can be eliminated.
 - Compared to OTC remedies, Aphthasol is considered more effective and more likely to “heal” ulcers.
 - Better tasting, more likely to adhere and provides a protective barrier compared to Kenalog in Orabase.

AMLEXANOX PHARMACOLOGY

- ❑ Potent anti-allergic effect demonstrated in a variety of *in vivo* models.

- ❑ Potent inhibitor of the release of inflammatory mediators from mast cells.
 - Antigen - antibody induced release
 - Ionophore induced release

- ❑ Potent inhibitor of generation of 5- and 12- lipoxygenase products in whole tissue studies.

- ❑ Inhibits formation of leukotrienes - *in vitro*.

- ❑ Does not inhibit generation of cyclo-oxygenase products in whole tissue studies.

- ❑ Potent inhibitor of cyclic nucleotide phosphodiesterase.

- ❑ Inhibits *in vivo* - bronchoconstriction induced by:
 - LTD 4 (leukotriene)
 - PAF
 - Antigen

- ❑ Has no effect on bronchoconstriction induced by histamine or acetylcholine.

- ❑ Weak anti-inflammatory activity *in vivo*.

AMLEXANOX TOXICOLOGY

Studies completed include:

- 1% and 2% oral rinse assessed in an oral mucosa irritation study in rats.
- 5% paste irritation study in hamster cheek pouch and human subjects.
- Human dermal sensitization study.
- Systemic toxicity assessed in a variety of single and multiple dose studies.
- Reproduction
- Mutagenicity
- Carcinogenicity

Conclusion:

Animal studies have indicated that amlexanox has a large margin of safety for use in the treatment of canker sores. Evaluation of the sensitization potential using topical application indicate no significant sensitization risk to patients. There were no negative reproduction, mutagenicity or carcinogenicity findings with amlexanox.

AMLEXANOX 5% PASTE CLINICAL DATA SUMMARY

Amlexanox Vs. No Treatment

Treatment Day	<u>% of Subjects with Completely Healed Ulcers</u>		<u>% of Subjects with Complete Pain Resolution</u>	
	5% Amlexanox	No Treatment	5% Amlexanox	No Treatment
2	6.6	2.6	20.3*	10.8
3	21.3*	8.2	43.7*	21.7
4	37.9*	22.3	60.5*	39.3
5	52.1*	33.3	74.4*	55.4
6	65.6*	47.5	83.1*	65.6
Median days to heal/ Complete Resolution	4.8*	6.4	3.3*	4.6
Log Rank Statistic	P value	<0.001	P value	<0.001

Amlexanox Vs. Vehicle

Treatment Day	<u>% of Subjects with Completely Healed Ulcers</u>		<u>% of Subjects with Complete Pain Resolution</u>	
	5% Amlexanox	Vehicle	5% Amlexanox	Vehicle
2	5.2	5.0	20.0	15.9
3	18.0	16.2	42.5*	35.6
4	37.4*	26.7	59.8*	48.6
5	51.1*	41.8	74.1*	62.3
6	67.4*	54.7	82.8*	72.8
Median days to heal/ Complete Resolution	4.9*	5.6	3.4*	4.1
Log Rank Statistic	P value	<0.001	P value	<0.001

*Significantly better than no treatment or vehicle at the .05 level.

AMLEXANOX 5% PASTE EFFICACY SUMMARY

5% Amlexanox Compared to No Treatment

- ❑ Accelerates Healing of Aphthous Ulcer
 - 72% faster rate of ulcer healing
 - Shorter median time to heal
- ❑ Accelerates Complete Resolution of Pain
 - 90% faster rate of pain resolution
 - Shorter median time to complete pain resolution
- ❑ Effective for Treatment of Aphthous Ulcers
 - Greater percent of patients with complete resolution of pain and healed ulcers on specific days

5% Amlexanox Compared to Vehicle

- ❑ Accelerates Healing of Aphthous Ulcer
 - 39% faster rate of ulcer(s) healing
 - Shorter median time to heal
- ❑ Accelerates Complete Resolution of Pain
 - 34% faster rate of pain resolution
 - Shorter median time to complete pain resolution
- ❑ Effective for Treatment of Aphthous Ulcers
 - Greater percent of patients with complete resolution of pain and healed ulcers on specific days

AMLEXANOX 5% PASTE COMPARISON OF CLINICAL DATA

Reported studies on other materials topically applied to aphthous ulcers have demonstrated rather unremarkable results in accelerating healing.

- ❑ Mean healing times for commercially available Orabase have been reported as 7.8 days (Plemons JM, Rees TD, Binnie WH, Wright JM, Guo I, Hall JE. Evaluation of acemannan in the treatment of recurrent aphthous stomatitis. Wounds 1994;6:40-5).

- ❑ Corticosteroid in Orabase has been reported as being equally effective as Orabase (Stoy PJ. The use of topical applications in the treatment of inflammatory conditions of the oral mucosa. Dent Pract 1966;16:444-7).

- ❑ Triamcinolone in Orabase has been reported to have some subjective improvement; however, some studies indicate that they were unable to demonstrate any significant benefit in healing (Browne RM, Fox EC, Anderson RJ. Topical triamcinolone in recurrent aphthous stomatitis. Lancet 1968;(March 16):565-7).

- ❑ Ora-5 has been reported to decrease both pain and ulcer size, but mean ulcer duration in the treated group was over 7days, and the pain in the treated group increased between day 5 and 8 (Dale RA, Berrong JM, Sandoval VA, Duke ES, Dodge WW. The use of Ora-5 on recurrent aphthous ulcers. Gen Dent 1989;(Nov-Dec):504-7).

The beneficial effect of amlexanox 5% paste to accelerate the healing of aphthous ulcers has been clearly and consistently demonstrated in the four similarly designed, vehicle-controlled studies, representing the largest clinical program reported for this condition.

AMLEXANOX 5% PASTE

PRODUCT SUMMARY

- ❑ Product competes in a large unsatisfied market place.

- ❑ The only product supported by adequate and well-controlled clinical studies with therapeutic claims.

- ❑ Effectively treats aphthous ulcers:
 - Accelerates healing
 - Accelerates complete resolution of pain

- ❑ Minimal side effects at the site of application with no systemic side effects.

- ❑ Well accepted by patients in clinical studies.

- ❑ Large percentage of study patients would purchase the product.

- ❑ Meets the physician's desired product profile.

AMLEXANOX NEW PRODUCT DEVELOPMENT

ORADISC™

ACCESS is developing OraDisc™, a biodegradable mucoadhesive disc incorporating amlexanox for the prevention and treatment of aphthous ulcers. Applying conventional paste and gel formulations and keeping them in place over time is sometimes difficult, thereby reducing patient compliance and limiting the effectiveness of drugs for oral conditions.

OraDisc™ is a “dime sized” solid dosage form used to deliver amlexanox to the mucosal tissue. The thin, flexible, biodegradable bilayer polymer film is composed of a backing layer attached to a layer which contains both the mucosal adhesive polymers and amlexanox. The film is cut into circular 1/2" discs containing 2 mg of drug, which is estimated to be the equivalent dose currently being administered in the paste form. Once in contact with the mucosal tissue, the properties of the mucoadhesive polymers assure the adhesion of the film to the moist mucosa. While adhering to the mucosal tissue, the polymer absorbs moisture, commences disintegration and local release of amlexanox at the site of application. Complete erosion and drug release occurs in less than 60 minutes with any remaining materials washed away in normal saliva flow and swallowed.

OraDisc™ is anticipated to provide a more controlled delivery of amlexanox because:

- The disc will limit delivery of amlexanox to a small surface area.
- The backing will help retain the active substance at the site of the aphthous ulcer for a longer period.

Utilizing this technology, it is anticipated that higher drug concentrations will be achieved at the site of administration increasing the effectiveness of the product.

The discs are also expected to be more acceptable to the patient in terms of ease of application and cosmetic properties.

The inactive ingredients of OraDisc™ are classified as generally regarded as safe (GRAS) which has significantly reduced the development time and the development costs.

ORADISC™

PRODUCT DEVELOPMENT STATUS

- ❑ CTX (United Kingdom) and IND (US) applications filed with the respective regulatory authorities.

- ❑ Phase I, 72 hour multiple skin application irritancy study completed in the US.

- ❑ Pilot Phase II punch biopsy wound healing study in healthy volunteers comparing OraDisc™ to placebo and no treatment, completed in Northern Ireland with statistical significance achieved compared to both placebo and no treatment.

- ❑ Phase III study completed in Northern Ireland to demonstrating the ability of OraDisc™ to prevent the formation of ulcers when applied at the first sign or symptom of the disease.

- ❑ A Phase III multi-center treatment of aphthous ulcer study is planned to commence in the 1st Q of 2002 in 25 sites in the US. There will be an active, placebo and no treatment arms in the study, which will enroll approximately 700 patients. Completion is anticipated in the 3rd Q of 2002 with market approval estimated in the 3rd Q of 2003.

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