CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Medical Review(s)

Multi-Disciplinary Summary
NDA 21-727 TRADENAME (amlexanox 2 mg mucoadhesive oral patch)

Treatment of [ ] of aphthous ulcers in adults and adolescents 12 years of age and older

September 23, 2004

This new NDA for TRADENAME (amlexanox 2 mg mucoadhesive oral patch) for the treatment of [ ] of aphthous ulcers in adults and adolescents 12 years of age and older is recommended for approval by the review team.

CMC:

Recommendations by the CMC reviewer were limited to minor, but helpful, labeling issues. In particular, the stability data submitted by the sponsor did not support the storage conditions, which had to be revised in the label.

Pharm/Tox:

The submission contained no new nonclinical data, and referenced NDA 20-511 for Aphthasol®, the approved amlexanox 5% paste formulation approved in 1996. The reviewer recommended Pregnancy Category B. The reviewer further concluded that no toxicity relevant to the proposed clinical use was observed, and there are no nonclinical safety issues relevant to clinical use.

Biopharmaceutics:

The Pharmacokinetics of this product were assessed in a Phase 1 single-dose study, a Phase 3 multi-dose study and a Phase 1 study that evaluated the effects of amlexanox on the cytochrome P450 system. In addition, clinical safety data is available from the Aphthasol® paste formulation and the oral tablet formulation that is approved in Japan.

Amlexanox is absorbed largely through the GI tract. It was determined that absorption through the ulcer was insignificant. Amlexanox has a half-life of 3-6 hours and only 17% is eliminated through the kidney. There a no significant concerns in using this product in people with hepatic or renal limitations.

TRADENAME was demonstrated to have a relatively minor effect on various CYP450 isozymes (< 10 % inhibition or stimulation), and is therefore unlikely to have a significant effect on drugs and xenobiotics metabolized through the CYP450 pathway.

Clinical Safety:

Adverse events observed in clinical trials with this product were infrequent and non-serious.

Clinical Efficacy and Biostatistics:

This reviewer agrees with Dr. Hyman's clinical review on all points. However a clarification needs to be made about the extent to which approval is based on findings from studies using the early formulation. While Dr. Hyman has not specifically referred to the data from the early formulation as "supportive," he does refer to that data at various points in his review. In particular, his discussion of the non-inferiority comparison between vehicle and no treatment refers to data from the Phase 3 trial using the early formulation. He also refers to the data from the same trial in his discussion of efficacy in adolescents age 12 – 17. For the record, the Division has concluded that the two formulations are different enough that they cannot be considered "the same" absent a bioequivalence study to demonstrate that they are the same. No study has been conducted; therefore the data from the studies of the early formulation cannot be used to support the Agency's finding of efficacy for this product.

The Division views this product as a line extension of the approved product Aphthasol® (amlexanox oral paste), 5 mg, and consequently agreed to accept a single study to support efficacy. The agreed upon criteria for success were that the active had to be statistically significantly superior to the vehicle and the vehicle had to be non-inferior to no treatment. The pre-specified non-inferiority margin was -8%. These criteria for success were based on FDA's draft guidance document, *Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment.* As was discussed in both Dr. Hyman's clinical review and in the Biostatistics review, the non-inferiority comparison between vehicle and no treatment (-9.2%) was close, but fell slightly outside the pre-specified non-inferiority margin (-8%). However, it should be noted that the point estimates for the vehicle and no treatment arms were very close (21.9% for vehicle v. 21.6% for no treatment), which supports the fact that the vehicle is not deleterious. In addition, the small number of patients in the no treatment group make it difficult to show a difference between groups.

This reviewer feels that the failure to meet this criterion should not result in failure to approve this product. I recommend approval for this NDA.

Recommendation:

In summary, all disciplines have recommended that this new dosage form for amlexanox be approved. The sponsor has agreed to the labeling attached to Dr. Hyman's clinical review.

John V. Kelsey, DDS, MBA
Lead Dental Officer

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/s/

John Kelsey
9/24/04 04:10:14 PM
MEDICAL OFFICER

Jonathan Wilkin
9/24/04 04:39:23 PM
MEDICAL OFFICER
I concur with the Dental TL that there is no need for reliance on data regarding the earlier patch formulation, and that there is sufficient information provided that the vehicle is not deleterious.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-727
Submission Code	N-000
Letter Date	December 4, 2003
Stamp Date	December 9, 2003
PDUFA Goal Date	October 9, 2004
Reviewer Name	Frederick Hyman, DDS MPH
Review Completion Date	August 26, 2004
Established Name	Amlexanox
(Proposed) Trade Name	OraDisc™A
Therapeutic Class	Anti-inflammatory
Applicant	Access Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Adhesive Oral Patch
Dosing Regimen	One Patch q.i.d.
Indication	Treatment of[redacted] Aphthous Ulcers in Adults and Adolescents 12 Years of Age and Older
Intended Population	Adults and Adolescents 12 Years of Age and Older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

OraDiscA patch (2 mg amlexanox in a mucoadhesive patch) has shown adequate evidence of efficacy in the healing of aphthous ulcers. In one placebo-controlled, randomized and blinded clinical trial of seven days duration, a significantly higher percentage of aphthous ulcer patients experienced complete healing after four days of OraDiscA treatment compared to those who received a vehicle disk. Data from one additional non-pivotal phase 3 trial was also used to clarify two of the efficacy outcomes from the pivotal trial. OraDiscA has been shown to be safe for its intended use as recommended in the labeling by all means reasonably applicable to the assessment of safety. These include comparison of adverse events between groups in the clinical trials, reviewing laboratory data, reviewing postmarketing reports from already marketed amlexanox products, and gathering chronic use data from an open label safety trial. Demographic data allowed evaluation of safety and efficacy in subgroups based upon race, gender and age. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose. This new drug application is recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are being recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study commitments have been proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for the sponsor.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

OraDisc™A is the proposed trade name for an adhesive disk containing 2% amlexanox. Access Pharmaceuticals seeks approval of OraDiscA for the treatment of aphthous ulcers when applied topically to the ulcer site. The recommended duration of use is seven days for each aphthous ulcer occurrence. Amlexanox is not a new molecular entity, having been approved for the same indication in December 1996 as the active ingredient in Aphthasol®, an oral paste containing 5% amlexanox.

The clinical testing which formed the basis for evaluating safety and efficacy of OraDiscA consisted of three Phase 1 studies, one Phase 2 study, two Phase 3 trials and an open label safety study, for a total of 592 subjects assigned to either OraDisc, a vehicle patch, or no treatment. Of this total, 493 were exposed to amlexanox for seven days, and 99 were exposed to amlexanox for 28 consecutive days. Every subject who was exposed to OraDiscA in any of the clinical trials was included in the safety analysis, whereas the efficacy evaluation was based upon one pivotal phase 3 trial.

In addition to the above mentioned studies, the sponsor also relied upon data from marketed amlexanox products for additional safety support; these include not only Aphthasol as mentioned above, but also 50-mg amlexanox oral tablets that are approved in Japan for internal use as an agent to treat asthma and allergic rhinitis. Most of the pharmacology data and much of the biopharmaceutics data was gathered from the study of Aphthasol and resubmitted to this NDA. Postmarketing data from Aphthasol and the oral tablets were also submitted to this NDA in support of amlexanox safety.

1.3.2 Efficacy

Two phase 3 trials were conducted and submitted to this NDA. One of the phase 3 trials is considered pivotal for efficacy and the other phase 3 trial is not. The trials had identical efficacy endpoints, statistical analyses and evaluations; the non-pivotal phase 3 trial is not considered pivotal because it was conducted with an earlier formulation of OraDisc. The earlier formulation differed in the composition of the backing material from the final, to-be-marketed formulation of OraDiscA that was used in the pivotal trial.

The primary outcome variable for the efficacy trials is the percentage of subjects who had healed (defined *a priori* as all ulcers reaching the size of 0 mm) after four days of treatment. To achieve approval, it was specified that there be a statistically significant improvement of the percentage healed in the OraDiscA group compared to the vehicle group. In addition, the agreement between the sponsor and the Agency was that the percentage of subjects healed after four days on the vehicle treatment would be statistically non-inferior to the no-treatment group results. There are three secondary endpoints, which include 1) the number of days until healing 2) the percentage of patients with pain resolution after four days of treatment and 3) the number of days until pain resolution.

The study design was adequate with minimal opportunity for bias, and had adequate control groups, consisting of both a vehicle group and a no-treatment group. The trials were also sufficiently well-designed to allow the assessment of benefit; they were of adequate duration, employed appropriate entry criteria, tested an appropriate dose, and employed sound statistical analyses. Furthermore, the trial was successful in recruiting subjects of both genders, all age groups over 12 years, and all major U.S. racial groups.

Two problems arose during the review process which do not prevent approval, but did require additional evaluation. One flaw in the pivotal trial design is that it was underpowered for the non-inferiority comparison as pre-specified, due to an inaccurate

estimate of the expected results. The borderline demonstration of non-inferiority as set forth in statistical testing necessitated consideration of the stronger results in the non-pivotal trial. Another review difficulty was the interpretation of the secondary variables that examined pain relief. Whereas the efficacy results of the comparison between OraDiscA and the no treatment group demonstrated that OraDiscA contributes significantly to pain relief, the comparison of OraDiscA to vehicle disk does not reach statistical significance for pain relief. The pain relief that subjects experienced resulted from a combination of an increase in the percentage of subjects healed on Day 5 as well as the protective effect of OraDiscA to the ulcer site. The labeling should therefore reflect that subjects can expect pain relief in addition to healing while using OraDisc, but that amlexanox is not an analgesic.

The sponsor has adequately demonstrated that OraDiscA effectively increases the percentage of patients with aphthous ulcers who are healed at Day 5 compared to those who received a vehicle disk. They have also shown that the effect is valid, and was not caused by the vehicle exerting some detrimental effect on the aphthous ulcers. The effect was also valid in individuals with up to three concomitant ulcers.

OraDiscA will provide an additional therapy to the current armamentarium for treatment of aphthous ulcers. Current treatments include anti-inflammatory drugs, analgesic drugs, antimicrobial drugs and mucosal protectants. To date, the only drug that has been specifically approved to treat aphthous ulcers is Aphthasol, which is the 5% paste form of amlexanox. Although the results from OraDiscA appear similar to those of Aphthasol, no comparative testing was performed for efficacy, nor was comparative questioning on patient preference or ease of use evaluated.

1.3.3 Safety

A total of 592 subjects were exposed to OraDiscA in all studies. Of these, 493 completed studies in which they used OraDiscA for seven days and 99 subjects completed a long-term study in which they used OraDiscA for 28 days. The trials of seven days duration tested the drug for the recommended duration of application for each aphthous ulcer incident. Only the open-label safety study was long enough to simulate six months of use. Since most aphthous ulcer sufferers develop ulcers on a fairly regular basis, it is not unusual to be treated for a seven-day cycle 10-12 times per year.

Men and women, individuals of Caucasian, African American and Hispanic background, and adolescents from 12 – 17 were adequately represented. Patients who were excluded from the study such as diabetics and tobacco users do not limit the relevance of safety assessment, although their exclusion does leave concerns about generalizability of efficacy and will be addressed in the proposed labeling. There were no class effects evaluated, other than potential for local irritation from the topical drug products as a group.

There were no reports of death or other serious adverse events during any of the clinical trials. The most common adverse events reported were local irritation reactions such as

pain, irritation, and burning, which had incidences in the pooled safety studies of between 1% and 9%. Systemic events were mild and very few; they included nausea, sore throat, and headache. Since the incidence of these reactions is similar in the OraDiscA groups to the vehicle group, it is likely that the reported local events result from the physical presence of the disk more than from the amlexanox itself. There appears to be no significant potential for abuse or overdosage, or negative impact on growth or development. Because of the lack of data, it has been placed in pregnancy category B, with use during pregnancy and lactation recommend only if the benefit outweighs the risk.

Data gathered was adequate to assess safety, and included not only adverse event monitoring during the trials, but also pre-marketing and postmarketing evaluations for Aphthasol and postmarketing data that was available for oral amlexanox. Laboratory parameters were monitored during the open label study at baseline and during the final visit. Although there was no control group for comparison, the subjects were compared to their baseline values. There were very few shifts in lab values, and for those few, no cause for concern for patient safety was identified. Vital signs and ECG data were not collected during the clinical trials, but there was no reason to require this for a topical drug with a safe history.

One limitation of the data is that only 99 subjects were evaluated for chronic use of this drug - this is lower than the numbers suggested by the current ICH guidance on extent and duration of exposure needed to assess long-term safety. This smaller than ideal number is balanced against the very positive safety profile gathered from the long-term safety study as well as the profile from the approximately 500 subjects on Amlexanox in the normal seven-day cycle. In addition to that, the sponsor has submitted safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use.

The safety profile of OraDiscA is comparable to Aphthasol, the other currently approved treatment available for aphthous ulcers in the U.S.

1.3.4 Dosing Regimen and Administration

The appropriate dosing regimen is one OraDiscA patch applied directly to the aphthous ulcer four times per day until the ulcer heals. This was the only dosing regimen tested in the clinical trials and is the same dosing as the approved amlexanox product, Aphthasol.

1.3.5 Drug-Drug Interactions

No drug-drug interactions have been identified.

1.3.6 Special Populations

OraDiscA was tested in children between the ages of 12 and 17. Although the safety data were adequate to conclude that it is safe for use in children of this age, the sample size was too small in this age group to be conclusive about the efficacy data in children.

However, due to the lack of literature to suggest that aphthous ulcers in adolescents behave differently than in adults, the Agency believes that efficacy can be extrapolated from the adult data. The pediatric section of the label will be written to reflect the trial results for pediatric patients.

2 INTRODUCTION AND BACKGROUND

Aphthous ulcers are small, round to ovoid lesions, generally less than five millimeters in diameter, which are found mainly on the non-keratinized, mobile mucosa of the lips, cheeks, floor of the mouth, and tongue. The ulcers are flat, are covered with a gray-white pseudomembrane of fibrin and other debris, and are surrounded by a raised erythematous rim. They can be divided into three classes:

- Minor aphthae: Single minor (less than 10 mm) lesions are by far the most common presentation. Such lesions heal in one to two weeks. Some patients have multiple minor lesions. Although individual lesions heal in one to two weeks, new lesions may appear as the old ones are healing.
- Major aphthae: Major aphthae are lesions of over 10 mm in diameter and may occur in any area of the mouth. They last up to six weeks and, unlike minor aphthae, heal with scarring.
- Herpetiform ulcers: The least common form of aphthous ulcers is herpetiform ulcers, which occur as multiple small clusters of pinpoint ulcers. Although the lesions are herpes-like in appearance, herpes simplex virus cannot be cultured from them.

Unless otherwise noted in the remainder of this review, all references to aphthous ulcers means "minor aphthae." Although exact numbers vary depending upon the source, aphthous ulcers are a common phenomenon with an incidence of approximately 50% in the general population. Most literature reports that approximately 50% of men have reported a history of aphthous ulcers as have 57% of women. A survey conducted by the National Institutes of Dental and Craniofacial Research cites the number of school-age children reporting a history of recurrent aphthous ulcers as 37%. A genetic predisposition to this condition, which occurs in otherwise healthy people, has been demonstrated through population studies and twin studies.

In addition to appearing in healthy individuals, aphthous ulcers also appear in some diseases, notably AIDS, Behçet's syndrome, and inflammatory bowel disease, and in some deficiency states, such as iron or folate deficiency. Tobacco users have been reported to be less likely to develop aphthous ulcers than is the general population (Grady, Ernster, Stillman, and Greenspan, 1992).

Aphthous ulcers are thought to be formed through a T cell attack on some unidentified epidermal antigen. The triggering event for the T cell attack is not known. A number of attempts have been made to detect the presence in the ulcer of viruses or of aberrant, intracellular forms of bacteria that might be the source of antigen triggering the attack. The results of these studies have been almost uniformly negative, although such a source of antigen cannot be completely ruled out.

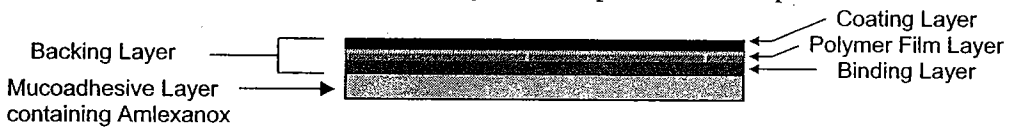
Trauma is known to cause aphthous ulcer formation in individuals who are predisposed to them. It is believed that if simple trauma can initiate an aphthous ulcer in susceptible

individuals, some imbalance in the immune system must allow the ulcer to occur, instead of the normal sequence of inflammation and healing. Several differences have been found between aphthous ulcers and "ulcers" induced by trauma in normal individuals. Compared to traumatic ulcers, aphthous ulcers contain three and a half times more TNF alpha-containing cells; more adhesion molecules; 60% more mast cells; 50% more XIIIa+ cells; and seven times more gamma/delta T cells.

2.1 Product Information

OraDisc™A is the proposed trade name for a mucoadhesive disk containing 2% amlexanox. Access Pharmaceuticals seeks approval of OraDiscA for treatment of aphthous ulcers when applied topically to the ulcer site. Amlexanox is not a new molecular entity, having been approved as the active ingredient in Aphthasol®, an oral paste containing 5% amlexanox. Aphthasol was approved on December 17, 1996 as NDA 20-511 for the treatment of signs and symptoms of aphthous ulcers in immunocompetent individuals. The dosage for Aphthasol paste is ¼ inch of paste (containing 2 mg of amlexanox) applied four times per day to the ulcer site. The proposed dosage for OraDiscA is one patch (containing 2 mg of amlexanox) applied four times per day to the ulcer site. Although the dosage of active ingredient is identical, a new delivery system necessitates a new NDA.

OraDiscA is an adhesive wafer of ½" diameter with very little thickness (275 μm). One side of the disk contains a 3-layered cellulose backing. The other side of the disk contains amlexanox in a mucoadhesive layer that is placed on the aphthous ulcer.



Amlexanox is 2-amino-7-isopropyl-5-oxo-1H-(l)benzopyrano-(2,3-b)pyridine-3-carboxylic acid. It has been shown to have anti-allergic activity, to inhibit bronchoconstriction, and to have some anti-inflammatory effects in models for both chronic and acute inflammation. Although the sponsor has stated in this submission that the exact mechanism of action in healing aphthous ulcers is not known, both *in vivo* and *in vitro* studies of the mechanism of action of amlexanox have indicated that the agent has the following mechanisms of action:

- Inhibition of the immunologically-stimulated release of histamine from mast cells.
- Inhibition of leukotriene D_4 generation.

The applicant's proposed indication is "OraDisc ™A (Amlexanox 2 mg, Mucoadhesive Patch) is indicated for the treatment of [ ]aphthous ulcers in adults and adolescents 12 years of age and older."

The 2-mg patch of amlexanox is the only dose of OraDiscA proposed, and the dosing regimen is one patch placed on the area affected by the aphthous ulcer four times per day. Although most individuals only experience one aphthous ulcer at a time, for those who experience multiple concurrent aphthous ulcers, the drug is proposed to be used to treat up to three ulcers at one time.

2.2 Currently Available Treatment for Indications

The treatments used for aphthous ulcers can be divided into four categories: Anti-inflammatory drugs, analgesic drugs, antimicrobials drugs, and mucosal protectants.

Anti-inflammatory drugs

- Corticosteroids: Steroids are a standard treatment for many types of inflammation. They are mainly used topically for aphthous ulcers, but in severe cases, oral steroids are sometimes given short-term. Steroids, however, even when used topically, have side effects that limit indiscriminate use.
- Thalidomide: Treatment of Aphthous ulcers is not a labeled indication for thalidomide. However, it is used to treat long-standing serious major aphthous ulcers, mainly in AIDS patients. This drug has serious toxic effects, neuropathy in particular, and is a strong teratogen.
- Amlexanox: Amlexanox is applied topically, currently available as Aphthasol 5% amlexanox paste.

Analgesic drugs

- Local anesthetics: Local anesthetics are the ingredients used in over-the-counter drugs for aphthous ulcers. They must be applied repeatedly for continuous pain relief.
- Acetaminophen and NSAIDs are sometimes used systemically for the relief of aphthous ulcer pain.

Antimicrobial drugs

- Chlorhexidine rinses are labeled for treatment of gingivitis, but are sometimes prescribed off-label as an aid in reducing bacteria in the mouth with the hopes of reducing severity of aphthous ulcers. It has not been scientifically demonstrated to be effective for aphthous ulcer treatment or prevention.
- Tetracycline is used topically as a rinse or paste, also an off-label use. Although not validated, its action on aphthous ulcers is thought to be due to its inhibition of metalloproteinases.

Mucosal Protectants

- Carboxycellulose is an acrylic covering used after dental procedures to cover abrasions and incisions. It is sometimes used to coat aphthous ulcers.

2.3 Availability of Proposed Active Ingredient in the United States

Amlexanox is marketed in the US as a 5% oral paste formulation in Aphthasol®, which was approved by the U.S. Food and Drug Administration for the treatment of aphthous ulcers in 1996. Section 2.1 of this review supplies a brief description of the labeling and dosing of Aphthasol. In the United States, there have been no major safety concerns or labeling changes for Aphthasol. Because Aphthasol was approved in the Division of Dermatologic and Dental Drug Products, the Division is familiar with the product. There were no serious safety issues during the approval process for Aphthasol, and the knowledge of its safety profile has been very helpful in the drug development of OraDiscA to both the sponsor in gathering safety data and the Agency for evaluating it. In terms of efficacy, the determination of clinical benefit of the observed treatment was discussed in depth. From those past deliberations, both the Agency and the Sponsor were better aware of selecting outcome variables that presented the most realistic evaluation of the drug's effect and how to report it for easiest interpretation and analysis.

2.4 Important Issues With Pharmacologically Related Products

Amlexanox is an anti-inflammatory drug which inhibits leukotriene and histamine. In order to compare amlexanox to similar products, it is first necessary to note that amlexanox, as well as pharmacologically-related products, have a history in the world marketplace for systemic use. It would be expected that OraDiscA's 2 mg of amlexanox per dose - acting topically until disintegrated and being ingested - would exert very little systemic effect compared to ingestion of 50 mg per dose. Nonetheless, systemic absorption is valuable background information in evaluating adverse events that emerge in OraDiscA's trials, and is useful to note should a future safety signal arise. Therefore, for completeness, these pharmacologically related products that are used internally will be examined. Following that discussion, the remainder of this section will examine relevant issues with two related groups of drugs: 1) topical products, and 2) drugs delivered through an oral patch.

Amlexanox is available in Japan as an oral tablet containing either 25 mg or 50 mg of active ingredient, where Takeda Pharmaceuticals markets it for the treatment of bronchial asthma (approved in 1987) and allergic rhinitis (approved in 1989). Takeda Pharmaceuticals also produces amlexanox in a nasal solution of 0.25%, which is marketed in Japan for the treatment of allergic rhinitis (approved in 1988). Senju Pharmaceuticals markets amlexanox in an ophthalmic solution of 0.25% in Japan for the treatment of allergic conjunctivitis (approved in 1989). There is very little literature about the mechanism of action or adverse events profile associated with the Japanese use of amlexanox when taken internally. However, Amlexanox very closely resembles another leukotriene inhibitor, sodium cromoglicate, which has been well-studied in terms of adverse events and toxicity. Sodium cromoglicate is not marketed in the United States, but is widely available in Europe. Martindale includes a detailed review of sodium cromoglicate, which is administered by mouth at a dose of 25 or 50 mg three

times daily for the management of asthma and allergic rhinitis. Most of these effects discussed here are therefore associated with an amlexanox-related drug taken internally at 10 – 20 times the dosage for OraDiscA.

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions, which have sometimes occurred after treatment for several weeks or months, include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe reactions such as marked bronchospasm, laryngeal edema, angioedema, and anaphylaxis have been reported rarely; these have sometimes been referred to as pseudo-allergic.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pain have occurred when it is taken by mouth. Transient burning and stinging have occasionally been reported following use of sodium cromoglicate eye drops.

The topical drug products, as a group, often share the common concern of local irritation. Therefore, a thorough examination of local irritation and sensitization was performed for OraDiscA, both through animal toxicology studies and evaluation of human experience. Results of oral, ophthalmic, and dermal irritation as well as sensitization studies revealed no safety concerns that warrant further testing. Refer to Section 3.2 (Animal Pharmacology/Toxicology) and Section 7.1.5 (Common Adverse Events) of this review for further detail on those studies.

Because of this product's unique delivery system as an oral adhesive patch, a drug with a very similar delivery system is noted here. Striant® Testosterone buccal system is a delivery system for testosterone that when applied to the buccal mucosa, slowly releases testosterone, allowing for absorption of testosterone through gum and cheek surfaces that are in contact with the buccal system. Since venous drainage from the mouth is to the superior vena cava, trans-buccal delivery of testosterone circumvents first-pass (hepatic) metabolism. The patches differ from OraDiscA, therefore, in that Striant is designed to remain intact for 12 hours, at which time it is removed and replaced with a new patch whereas OraDiscA is designed to dissolve into a paste within one – two hours, and ultimately be swallowed. Although OraDiscA does not achieve its action through systemic action, the Agency recognizes through the example of Striant how easily oral patches can be absorbed into the circulation. As a result, the amount of amlexanox absorbed via the buccal route versus through ingestion was examined through pharmacokinetics studies (Refer to Section 5 - Clinical Pharmacology). It is noteworthy that the most common adverse event associated with Striant is oral irritation at the site of placement with an incidence of approximately 10%. To ascertain that the potential for local irritation of OraDiscA could not negate the effects of amlexanox on healing, the sponsor designed the trial with a vehicle arm and a no treatment arm. One of the primary outcome variables is a comparison of vehicle to no treatment to demonstrate that the

OraDiscA vehicle is not detrimental to healing of the aphthous ulcer when compared to no treatment.

2.5 Presubmission Regulatory Activity

A pre-IND meeting was held on November 10, 1999 during which several general guidance questions were proposed by the sponsor and answered by the Agency . The IND for OraDiscA was opened on March 2, 2000 and assigned number 59,949. Comments were provided to the sponsor by the Agency about details of the proposed protocol, but there were no safety issues that prevented or delayed initiating trials under the IND. The sponsor's initial study plan included a proposed endpoint of complete pain resolution. The Agency suggested complete resolution of the ulcer as a better endpoint for the proposed indication and the sponsor concurred.

Just prior to conducting their pivotal trial, the sponsor made a decision regarding a formulation change that had major regulatory impact. There was an earlier formulation of the disk containing a [ ] backing that needed to be peeled from the disk prior to placement. The new, to be marketed, formulation eliminated the [ ] layer, and instead substituted a cellulose film that dissolves during use and therefore is not removed before disk placement. The early formulation had been used in Phase 1 and Phase 2 trials, including a trial that the sponsor called a "phase2/3 study." When the sponsor submitted the protocol for the Phase 2/3 study, they had been advised by the Division to request an EOP2 meeting before proceeding with any phase 3 trials. They had declined, stating that the Phase 2/3 trial was not intended to be pivotal.

When the sponsor requested and was granted an EOP 2 meeting, held on August 20, 2001, the final to-be-marketed formulation was proposed for use in the phase 3 pivotal trial. One of the questions that the sponsor asked of the Agency in the EOP2 meeting package was whether the already-completed Phase 2/3 trial could be regarded as pivotal. The Agency informed the sponsor that the new to-be-marketed formulation is sufficiently different from the old formulation that results from studies with the older formulation would not be considered pivotal towards approval. The Agency further stated that if the sponsor would only be submitting one pivotal trial with the new formulation, it would be expected to be "very persuasive with robust results and no significant flaws" to gain approval (exact quote from EOP2 meeting minutes).

Also during the EOP2 meeting, the Agency provided the sponsor with several clinical comments about their proposed Phase 3 pivotal study. As a result, the sponsor revised their Phase 3 protocol and submitted it as a 45-day special protocol assessment (SPA) on December 20, 2001. The Agency reviewed the SPA and gave comments, which the sponsor responded with a revised phase 3 protocol for concurrence. Based upon the comments made during the EOP2 meeting, and the comments provided during the SPA review and its follow-up, the following agreements were made between the sponsor and the Agency:

1. To fulfill the pediatric requirement, subjects would be enrolled between the ages of 12 and 17, with 25% of the subjects between the ages of 12 and 14.
2. To more adequately assess adverse events, the sponsor would ask specific questions, rather than rely on broad spontaneous reporting. They revised the protocol by adding two questions as follows: "Have you noticed any change in your health since the last visit?" and "Did you experience any pain or discomfort when using the patches?" They also queried the subjects about ease of application and whether the patch remained in place on a 0-10 scale. The sponsor also proposed a separate study of 18 subjects to measure the erosion of the patch and whether loose particles were common during use.
3. The sponsor originally proposed to treat and follow only one ulcer, even if more than one was present at the time of study enrollment, but changed the protocol to comply with the Agency's comment. The Agency had advised allowing for evaluating up to 3 concomitant ulcers should subjects present with them, to mimic the actual use conditions.
4. The Agency clarified that the "win" criterion would be that the percentage of aphthous ulcers that resolved with amlexanox disk would be statistically superior to the percentage of aphthous ulcers that resolved with vehicle disk. The second condition of win would be that the vehicle is not inferior to no treatment to which the sponsor agreed and proposed a 97.5% one-sided lower confidence interval of -8%.
5. The Agency offered to defer until Phase 4 demonstration of safety in 300-600 subjects on active for at least six months. The sponsor declined the offer and stated that they would submit 6-month safety data with the NDA.

At a guidance meeting held on August 13, 2003, shortly prior to filing the NDA, the sponsor asked for Agency concurrence that their Phase 3 study was very persuasive. The agency responded that on the surface, the results did not appear very persuasive, but that it would be a review issue should the sponsor file the NDA. The Agency suggested a [ ] With a successful outcome, the results of studies with the old formulation could be considered towards NDA approval. The sponsor proposed [ ] The sponsor planned [ ]

After discussion during an internal midcycle review meeting held on May 25, 2004, it was decided that one successful pivotal study that could demonstrate safety and efficacy of the drug would be sufficient. This was based upon the decision that this new drug was a new delivery system of an already marketed drug containing the already approved dose. A relevant CDER Guidance for Industry entitled, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, Section II.C.2a.: "Different doses, regimens, or dosage forms" was cited and states the following:

"It may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness or a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient."

Since the effect of the drug is topical, pharmacokinetic data alone is not sufficient to assess the local effect. Because both the OraDiscA form of amlexanox and Aphthasol paste are labeled to deliver 2 mg of amlexanox to the aphthous ulcer four times per day, OraDiscA is appropriate for regulation under this guidance document. The Agency decided that one pivotal trial would be sufficient with standard criteria for persuasiveness. The sponsor was informed by t-con of May 28, 2004 that, after extensive discussion, it had been decided that the additional studies would not be required and that the Agency could complete its review without them.

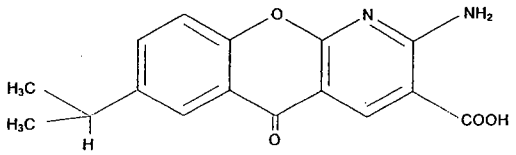
2.6 Other Relevant Background Information

In section 2.4 of this review the approval of amlexanox tablets in Japan for treatment of allergic rhinitis, allergic conjunctivitis, and for asthma has been discussed. The adverse events profile of amlexanox as used for these indications is discussed in section 7.1.17. It has also been pointed out in both of those sections that the dose of amlexanox as taken internally is approximately 20 times the dose that is delivered in the OraDiscA. Information from this foreign marketing does not raise concerns about the approval of OraDiscA.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

OraDisc™A is a mucoadhesive patch that 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, and sodium carboxymethylcellulose.
Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2, 3-b] pyridine-3-carboxylic acid.
Structural formula



Empirical Formula: $C_{16}H_{14}N_2O_4$
Molecular Weight: 298.30
Physicochemical Properties: Amlexanox is an odorless, white to yellowish-white crystalline powder insoluble in water.

The CMC reviewer has uncovered a problem with the sponsor's proposed labeling for drug stability. The analytical results identify a lack of 12-month stability at [redacted] although the proposed label recommends storage at up to that temperature. The data does however, support adequate stability at up to 25° C. The labeling will be modified to reflect the correct storage conditions.

3.2 Animal Pharmacology/Toxicology

Little potential for toxicity was observed in a battery of toxicology studies conducted with amlexanox that included acute, subchronic, chronic, carcinogenicity, genetic, and reproductive studies. No-effect-levels (NOELs) in these studies were substantial multiples of the proposed human exposure.

The submission contained no new nonclinical data. The application references NDA 20-511, the application for Aphthosol 5% amlexanox paste, approved by FDA in 1998. NDA 20-511 contains the following nonclinical studies: acute toxicology, repeat dose toxicology, genetic toxicology, carcinogenicity, reproductive toxicology, and special toxicology including nasal cavity irritation, nasal mucosal irritation and an ocular irritation study. The drug is recommended for pregnancy category B through review of reproduction studies which 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). Those studies 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.

The pharmacology reviewer concluded that no toxicity relevant to the proposed clinical use was observed and there are no nonclinical safety issues relevant to clinical use.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data used in this review is the clinical trials conducted by the sponsor, Access Pharmaceuticals. Additional safety support also relies on data from the submission of Aphthasol amlexanox 5% cream, which Access Pharmaceuticals owns. (Block Drug company, which originally owned and sponsored Aphthasol, sold the product to Access shortly after approval.) Postmarketing safety data from Japan has also been submitted for products containing amlexanox that are approved there in higher dosages for oral ingestion to treat allergic rhinitis, allergic conjunctivitis and asthma, as well as in eye drops.

One consultation was requested by this Division for clinical microbiology. A clinical microbiologist from the Division of Anti-infective Drug Products (HFD-520) in FDA's Center for Drug Evaluation and Research submitted a written review, which is summarized in the Clinical Microbiology section of this review (Section 6.1.5) No Advisory Committee has been convened to discuss any component of this NDA review. Literature searches were performed, including through PubMed and Micromedix databases primarily to provide further information on safety.

4.2 Tables of Clinical Studies

	Study Title	Number of Subjects on Active	Number of Subjects on Vehicle	Number of Subjects on No Treatment	Safety Evalu-ations	Duration (Days)	Formulation (To-Be-Marketed) or Early
Phase 1 Clinical Trials							
AP-C-9E02	A Double-blind, Ramdomised, Vehicle-controlled, Parallel-group Study to Determine the Effects of Amlexanox Disc 2 mg in Preventing Recurrent Aphthous Ulcers in Patients Presenting at the Prodromal Stage	26	26	0	Day 4	4	Early
AP-C-9U05	A Phase I Study to Assess the Safety and Irritation Potential of OraDisc™A, 2 mg, and its Vehicle after Three 24-hour Occlusive Applications on the Skin of Healthy Volunteers	32	32	0		3	Early
Phase 2 and 3 and Open-Label Clinical Trials							
AP-C-1U106	A Phase 3 Evaluator-blinded, randomized, parallel-group Study to Determine the Effects of the Amlexanox 2 mg mucoadhesive Patch (OraDisc™A) on the Healing of Recurrent Minor Aphthous Ulcers as Compared with Vehicle Mucoadhesive Patches or No Treatment	303	301	97	Days 3,4,5,6 ,7	7	TBM
AP-C-9E03	A Phase2/3 Investigator-blind, Randomized, Parallel-group Study to Determine the Effects of Amlexanox Disc, 2 mg, (Early Formulation) on the Healing of Recurrent Aphthous Ulcers as Compared with Vehicle Discs or No Treatment	157	163	81	Days 3,4,5,6 ,7	7	Early
AP-C-2U108	An Open-Label, 28-Day Study to Evaluate the Long-term Safety of Amlexanox mucoadhesive Patch, OraDisc™ A 2 mg, in Patients with Recurrent Minor Aphthous Ulcers	106	0	0	Days 8, 15, 22, 29	28	TBM
Pharmacokinetics/Pharmacodynamics Trials							
AP-C-9E01	A phase 1, double-blind, randomized, vehicle-controlled study to Determine the Effects of Amlexanox OraDiscA, 2 mg, on healing of punch biopsy-induced wounds of the oral mucosa in healthy volunteers	11	9	20	1,2,3,6 ,8,10	10	Early
AP-C-1U107	A phase 1 study to investigate the pharmacokinetic characteristics of Amlexanox OraDiscA 2 mg, in 18 subjects with minor aphthous ulcers after a single application to 1 – 3 aphthous ulcers	18	0	0	0, 0.5, 1, 2, 3, 4, 6, 8, 10,12, and 24 hours post-dose	1	TBM

4.3 Review Strategy

Sources used for writing this review include all of the clinical studies listed above as well as results of studies submitted to NDA 20-511, Aphthasol (amlexanox 5% paste), and data from amlexanox 50-mg oral tablets. Only one of the clinical trials, AP-C-1U106 is considered a pivotal trial as was discussed in Section 2.5. The results of Study AP-C-9E03, a Phase 2/3 trial which used an older formulation, were examined to help clarify two review issues. One review issue is that one of the primary outcome variable

requirements for approval is demonstration of non inferiority of the vehicle to no treatment, which was borderline in its outcome in the pivotal trial. The second review issue was the efficacy question in children, which was inconclusive in the pivotal trial and therefore the pediatric data from the Phase 2/3 trial were also evaluated (Both to be discussed in detail Section 6.1.4).

The open label safety trial (AP-C-2U108) was the only trial which enrolled sufficient numbers of subjects for a long enough period to time to examine safety for chronic use; however, all subjects in all trials were monitored for safety and included in the safety reporting and analysis. Additional safety information was gathered from a review of results from the drug approvals and post-marketing information for Aphthasol paste and amlexanox 50-mg oral tablets. Approximately 800 subjects were treated with Aphthasol in clinical trials as a part of its development prior to the approval of its NDA. Post-marketing monitoring has included reports of adverse events between 1997 and the present. Over 1100 subjects were involved in pre-approval clinical studies in Japan in which the 50-mg tablets were administered for the treatment of asthma and allergic rhinitis. Data were collected for approximately 6400 patients from post-marketing safety surveys in Japan. The sponsor relied upon much of the biopharmaceutics evaluation of amlexanox from their studies conducted as part of their NDA submission for Aphthasol. Finally, data from Aphthasol and amlexanox tablets were submitted to help create the pharmacokinetics profile of Amlexanox.

4.4 Data Quality and Integrity

Early in the review process, a discussion between the Review Division and the Division of Scientific Investigations (DSI) was held to discuss the need for a site visit to audit any of the applicant's data and/or analyses. The discussion focused upon OraDiscA as a new delivery system for an identical dose of a drug that was approved in 1996 for the identical indication. Initial review of results from the various sites did not produce questions of unusual results at any particular center. The decision was mutually made that DSI would not schedule a site visit unless irregularities appeared as the review progressed. Similarly, there was no need for the review team or others (e.g., consultants, special government employees) to audit the case report forms (CRFs) or clinical source data.

4.5 Compliance with Good Clinical Practices

The content of the informed consent form was adequate and the sponsor obtained consent before enrollment into the trial as specified in the protocol. In terms of protocol violations, there were 18 subjects in the pivotal trial who had protocol violations, 15 of which were use of prohibited medications. One subject used two patches at each ulcer site, and was withdrawn from the study. One subject was diagnosed as having a Herpes Simplex Virus lesion, rather than an aphthous ulcer and was withdrawn form the study. One patient was randomized out of sequence. Fifteen subjects used medications during the study that were prohibited by the protocol, primarily oral analgesics – they were excluded from the efficacy evaluation.

One consideration that caused some discussion within the Division dealt with seven of the sites in the Phase 2/3 trial which were repeated in the pivotal trial, including use of the same investigators. The concern was that seven of the 23 sites used for the pivotal trial would have investigators who had already conducted this trial before, and therefore had the potential through their additional experience to give different outcomes than the remaining 16 sites. There was also concern that subjects may have been used twice at these sites. Evaluation of the results showed that no subjects who participated in the pivotal trial had participated in the Phase 2/3 trial. Nonetheless, the statistical reviewer did an analysis of the outcomes, examining results from the repeated sites separately. Interestingly, eliminating those seven sites from the overall analysis increased the success of the outcome of the pivotal trial significantly. The seven sites actually had results that had a greater "no treatment" effect than the other 16 sites. Because the pivotal trial was well-blinded and randomized, it is difficult to see how the investigators would be biased in their reporting.

4.6 Financial Disclosures

The sponsor has submitted to the NDA a completed and signed HHS Form FDA 3454 (Rev 6/02). In doing so, they have certified that "I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)." All investigators who participated in any of the trials during the IND development are listed. These arrangements do not raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

To assess the pharmacokinetics of OraDiscA, the Sponsor has conducted a Phase 1 single dose study (AP-C-1U107), a phase 1 pharmacology safety study to evaluate the effects of amlexanox on cytochrome P450, and a Phase 3 multiple dose study (AP-C-1U-106). In addition, clinical safety data of amlexanox from the oral paste and tablet formulations were supplied in this submission.

The basics of the pharmacokinetics of amlexanox were determined in the studies with amlexanox tablets. Systemically absorbed amlexanox is metabolized by hydroxylation to form the M-1 metabolite and some unidentified conjugates. The levels of M-1 metabolite were approximately 10% of the levels of amlexanox. There was no evidence of any accumulation of amlexanox or M-1 with multiple dosing. After a single oral application of 5 mg amlexanox, maximal serum levels of approximately 120 ng/ml were 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.

Study AP-C-1U07 supplied the following pharmacokinetics profile of OraDiscA in an adult population after a single application as follows:

Mean Pharmacokinetic Parameters Phase 1 Study AP-C-1U107

Parameter	One Patch 2 mg	Two Patches 4 mg	Three Patches 6 mg
Cmax (ng/mL)	N=14	N=1	N=3
Mean ±SD	45.4±39.6	138	168.3±191.5
Median (range)	39.8 [ ]		79.9 [ ]
Tmax (hr)	N=13	N=1	N=3
Mean ±SD	2.8±1.7	3	3.0±1.0
Median (range)	2 [ ]		3 [ ]
T_{lag} (hr)	N=13	N=1	N=3
Mean ±SD	1.0±0.6	1	1.0±0.9
Median (range)	1 [ ]		0.5 [ ]
AUC_{0-24} (ng·hr/mL)	N=14	N=1	N=3
Mean ±SD	258±238	475	605±356
Median (range)	226 [ ]		584 [ ]
$T_{1/2}$ (hr)	N=7	N=1	N=3
Mean ±SD	4.5±2.0	3.2	8.8±3.5
Median (range)	4.5 [ ]		10.3 [ ]

Based on the reported T_{lag} (0-1 hr) and mean T_{max} (~ 3 hours), there appears to be no or little absorption of amlexanox rapidly and directly through the aphthous ulcers. The lag time and T_{max} values indicate a slow erosion of OraDiscA, and a slow systemic absorption of amlexanox from the drug product.

Pivotal Trial AP-C-1U106 measured serum levels of amlexanox after multiple applications of OraDiscA. It also allowed subgrouping to examine pediatric pharmacokinetics and the difference between 1, 2, and 3 patches placed concurrently. The number of subjects in the adolescent population is too small (N=3) to give any statistically meaningful conclusion with respect to overall exposure of amlexanox in this population. Nevertheless, the mean amlexanox concentration in this group exhibits a similar trend to those in the adults.

Mean Pharmacokinetic Parameters, Phase 3 Study AP-C-1U106

Treatments	Amlexanox Serum Concentrations (ng/mL)	
	Prior to First Dose on Day 4	Two hours after First Dose on Day 4
All Patients		
Mean SD	16.0 ±31.7 (N=31)	20.9 ±24.1 (N=29)
Median (Range)	6.6 [ ]	14.8 [ ]
Pediatric Patients (N=3)		
	3.7± 5.2 (0-11.0)	13.5±12.3 [ ]
Patients Treated with One Patch, 4x daily		
Mean SD	9.8±16.5 (24)	15.8±16.4 (N=24)
Median (Range)	5.6 [ ]	11.5 [ ]
Patients Treated with Two Patches, 4x daily		
Mean SD	43.9±68.5 (N=5)	44.4±42.7 (N=5)
Median (Range)	10.0 [ ]	35.4 [ ]
Patients Treated with Three Patches, 4x daily		
Mean SD	20.4 (N=2)	18.6 (N=2)
Median (Range)	20.4 [ ]	18.6 [ ]

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.

The effects of amlexanox of CYP450 19, 1A2, 2C19, 2D6 and 3A4 were less than 10% inhibition or stimulation. Thus, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by those cytochrome P450 components. In addition, based upon the half-life of amlexanox (3-6 hours) and minimal renal elimination (17%), there is no significant safety concern in patients with renal or hepatic limitations for topical q.i.d. administration of OraDiscA.

5.2 Pharmacodynamics

The proposed mechanism of action is through histamine and leukotriene blockers. An early pharmacodynamics study showed that OraDiscA increased the rate of healing of biopsy wounds compared to contralateral wounds that received no treatment. However no pharmacodynamics studies were conducted to study the mechanism of action. Similarly, based upon the biopharmaceutical studies conducted for the approval of Aphthasol, there is no known effect of amlexanox on the QT interval and no know orthostatic effects or pharmacodynamic interactions. Therefore, no new studies were documented under this IND to evaluate those effects.

5.3 Exposure-Response Relationships

Based on NDA 20-511 for amlexanox paste, no new information has been submitted for the exposure-response relationships for the current mucoadhesive patch dosage form. The pharmacokinetics and pharmacodynamics of OraDiscA are consistent with those of Aphthasol. Since the dosing of drug substance is identical in OraDiscA to Aphthasol, the exposure-response relationships for efficacy are expected to be comparable to those in Aphthasol.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Aphthous Ulcers

Treatment of [ ] Aphthous Ulcers in Adults and Adolescents 12 years of Age and Older.

6.1.1 Methods

As was discussed in Section 2.5 of this review, only one pivotal trial is needed to support the efficacy component for the proposed indication, since OraDiscA is a new delivery system that contains the same active ingredient, at the same concentration, of an already marketed drug. This study, identified by the sponsor as AP-C-1U106, is a Phase 3 investigator-blind, randomized, placebo controlled trial which enrolled 701 subjects at 26 independent study sites.

The sponsor identifies Study AP-C-9E03 as a Phase2/3 trial. This study was conducted prior to the pivotal trial, and used an earlier formulation of the OraDiscA. Refer to section 2.5 of this review for a description of the differences in formulation and how the decision was made to consider this trial non-pivotal. Nonetheless, this earlier study has value in evaluating efficacy, as the protocols are nearly identical in both studies in study design, inclusionary and exclusionary criteria, endpoints, and results. In particular, the results from Study AP-C-9E03 will be persuasive in confirming the non-inferiority of the vehicle as will be discussed in detail in section 6.1.4.

6.1.2 General Discussion of Endpoints

The primary efficacy variable was identified in the protocol as the percentage of subjects who had healed (defined *a prioi* as all ulcers reaching the size of 0 mm) after 4 days of treatment (Day 5 of the study). In addition to the healing rate, pain resolution was also analyzed; however, as agreed upon during the End of Phase 2 meeting, pain resolution was identified as a secondary efficacy variable.

This choice of primary and secondary endpoints was based largely upon the conclusions of the trials of the previously approved amlexanox-containing product, Aphthasol. The clinical trials for Aphthasol employed both pain and healing as co-primary endpoints. Although the drug was approved based on a win of both, the pain relief results were difficult to interpret. Significant pain relief occurred on sporadic days during the trial,

and did not always correlate with significant healing as measured by ulcer size. To accurately reflect the outcome of the trials, the Aphthasol label states that "Pain relief occurred in conjunction with healing of the ulcers. Amlexanox oral paste, 5%, by itself, was not shown to be an analgesic medication." Based upon this past regulatory decision that amlexanox is not an analgesic, the Agency suggested that the sponsor use the percentage of subjects with complete healing as the primary outcome for OraDiscA, and evaluate the pain outcome as a sequel to the healing, and therefore secondary. The validity of the primary endpoint, percentage of subjects healed, was established during the approval process for Aphthasol. Data were submitted for related outcomes including comparison of the mean ulcer size between groups during the early days of the trial, and time to complete healing. Both of these analyses corroborated the result from the primary outcome variable.

Clinical benefit of the outcome was discussed at length during the deliberations on Aphthasol, and what was learned from that was applied during the regulatory process for OraDiscA. A clinically meaningful effect was not pre-specified in Aphthasol; any statistically significant improvement in the percentage of subjects healed with Aphthasol compared to vehicle was judged acceptable for approval. The relatively modest improvement in healing time seen (37% of subjects healed with Aphthasol compared to 27% of vehicle subjects healed at Day 4; average improvement in time to healing with Aphthasol was 1.6 days) was not a roadblock to approval since the safety profile for amlexanox is very good. For consistency between Aphthasol and OraDiscA, in which the same dose of amlexanox is proposed for the same indication, the same philosophy will apply to OraDiscA. The labeling will report the magnitude of effect, allowing the prescribing clinician and patient to make comparisons between the OraDiscA and Aphthasol, based upon their labels.

Access was advised very strongly by the Division to include a "no treatment" arm in the pivotal trial in addition to the vehicle arm, which they did. As was seen in the analysis of the Phase 2/3 trial, a vehicle possesses potential therapeutic value as a barrier to prevent insult to the ulcer. This vehicle could therefore affect the healing (primary endpoint) as well as pain relief (secondary endpoint) because of its ability to shield the ulcer. The agreement at the EOP2 meeting was that to demonstrate efficacy, the results would need to show a statistically significantly greater percentage of subjects who healed in the OraDiscA group compared to the vehicle group. It was also agreed that for an efficacy win, the placebo arm would have no worse efficacy than the no treatment arm. This was required to rule out the possibility that the OraDiscA arm could be superior to the vehicle arm due to the disk component of the total product causing irritation to the ulcer site, thus overstating the effect from the OraDiscA. The sponsor stated in a 45-day SPA that "the non-inferiority of vehicle to no treatment will be established if the lower confidence bound exceeds -8%."

The sponsor chose Day 5 as the time point for the primary endpoint evaluation largely as a result of reviewing Aphthasol's outcome and looking at early OraDiscA trials for the time to optimal improvement. Although this outcome seems appropriate, it is not without

potential shortcomings. For example, since the baseline requirement is an ulcer which has developed within 36 hours, there is the potential variation in subjects of 1.5 days for the baseline progression of ulcers, and that assumes that the self-reporting is always accurate. Therefore, an ulcer that has been present for 36 hours at baseline is quite likely to be healed by Day 5, even in the no treatment group. In addition, not all ulcers are the same size. Larger ulcers take longer to heal, so that a larger than average ulcer has a much smaller chance of healing by Day 5, and would be regarded as a failure, even if its healing rate is much better than a comparably sized ulcer on no treatment or vehicle. Randomization should minimize this potential problem by balancing the groups so that the sizes of the ulcers at baseline and the time at which the ulcer first appeared are evenly balanced.

In addition to this primary analysis of healing, the sponsor also proposed a secondary analysis of healing as corroboration and two other secondary endpoints which measure pain response. The alternative evaluation of healing is an analysis of time-to-healing, based on reaching ulcer size of 0 mm^2. Time-to-healing is defined for each patient as the number of days until healing if the ulcer healed on or before Day 7, or as a right-censored observation if the ulcer did not heal on or before Day 7. The time-to-healing distributions were compared among the three treatment groups using survival analysis as a secondary efficacy analysis.

The other two secondary efficacy variables are the percentage of patients with complete resolution of pain on study day 5 (defined as having reached pain score of <5 mm), and the time to healing based on pain score. To record the reduction in pain, subjects marked a 100-mm visual analogue scale (VAS) twice a day, which was anchored with a 0 at the far left for no pain, and a 100 at the far right for "worst pain imaginable."

6.1.3 Study Design

The pivotal trial, AP-C-1U106, meets the regulatory definition of adequate and well-controlled. The design, if executed according to protocol, is capable of assessing the benefit of OraDiscA. With respect to adequate and well-controlled studies, the trial:

1. Has minimal bias.
   The study has an OraDiscA group, a vehicle disk group, and a no treatment group. Although the subjects in the no treatment group could not be blinded, the evaluator does not know any individual subject's status. The primary outcome variable, measurement of ulcer size, is very objective and there is very little that the subject could do to influence this outcome. What is important is that the clinician who measures the size of the ulcer is blinded. Also helpful in minimizing bias is the presence of both a vehicle group and a no treatment group, so that the comparison of the vehicle to the OraDiscA group is blinded to both subject and investigator. The pain measurement is subjective, however, so that bias is quite likely between the no treatment group and the other two. As with the primary outcome evaluation, the presence of a vehicle group in addition to no

treatment allows a double-blinded comparison to assess the actual contribution from the active drug.

The win is set as the superiority of OraDiscA to vehicle disc. For non-inferiority testing, the vehicle is tested against no treatment with the purposes of demonstrating that the vehicle does not make the ulcer worse. It is unlikely that the subjects' knowledge of no treatment would influence the healing of the ulcer to any significant extent.

2. Has an adequate choice of control group
As was discussed in 6.1.2, the choice of primary and secondary endpoints was based upon results of Aphthasol studies and early OraDiscA trials. The OraDiscA studies did not need to rely on an historical control.

With respect to assessment of benefit, the pivotal trial:

1. Was of adequate duration
Seven days is the average length for healing of an aphthous ulcer. At baseline, an inclusion criterion dictated that the ulcer had to have developed within 36 hours. Since aphthae spontaneously heal in an average of one week, one would expect the difference between groups to become smaller as the end of the 7-day trial period approached, since the natural progression of the disease produces healing regardless of treatment. A trade-off had to be reached between giving the product sufficient time to have an effect, but not too much time, or the effectiveness would be difficult to determine. Based upon the greatest difference between groups being reached on Day 5 of the Aphthasol study, this time point was chosen by the applicant to be the time point for the primary outcome analysis for OraDiscA. One open label trial of 28 days duration was conducted to simulate several back-to-back treatment periods, but no efficacy measures were made during that trial. Those results will be discussed in the safety section of this review.

2. Employed Appropriate Entry criteria.
Patients were screened for the presence of aphthous ulcers and accepted only if the ulcer had appeared within 36 hours, which is appropriate for this proposed indication. Since it is not uncommon for patients to have concomitant ulcers (95% of chronic aphthous sufferers have reported having up to 3 aphthous ulcers concomitantly), subjects were enrolled with up to 3 ulcers.

3. Adequately chose the dosing
The dose chosen for OraDiscA was identical to the dose for aphthosol. The 2 mg of amlexanox in each OraDiscA corresponds to the approximate amount of amlexanox in one dab of 5% amlexanox paste, which is currently marketed in the United States. The proposed frequency of four times per day is also identical to the frequency that was proved efficacious for the amlexanox paste; the sponsor suggests that this is the highest frequency with which patients are likely to

comply. It would have been ideal to experiment with lower doses since it was expected that this OraDiscA new delivery system would be more efficient than the paste at supplying the same amount of amlexanox to the site and retaining it there longer. Nonetheless, amlexanox was shown in Aphthasol to have a very safe profile, and the Agency had no comments during the IND phase of development about exploring other dosing.

6.1.4 Efficacy Findings

In this section of the review, a detailed review of the results and analyses of the clinical studies that provide efficacy data for the proposed indication will be presented. A discussion of the demographic, baseline characteristics and inclusion/exclusion criteria pertinent to the efficacy evaluation is also included. The findings from the statistician's analysis of the data are integrated into the discussion. This section also includes a review of effectiveness data for gender, age, and racial subgroups.

The section also addresses limitations of the efficacy studies and describes how they have been resolved. For example, successful demonstration of safety and efficacy from one pivotal trial, 1U106, is sufficient for approval, as has been explained in Section 2.5, with reference to the FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. However, the results of Study 9E03, a Phase 2/3 study (sometimes referred to in this review as a non-pivotal phase 3 trial), is referenced in cases where the pivotal trial results alone are not conclusive.

Percent of Subjects healed on Day 5 - Primary Outcome variable

The primary outcome variable as pre-stated in the protocol is the percentage of patients who had healed (all ulcers size of 0 mm^2) after 4 days of treatment (Day 5 of the study). To win on this, it was agreed that there would be a statistically significantly greater percentage of subjects who were completely healed in the amlexanox group compared to those in the vehicle group. There must also be a demonstration that the outcome from the vehicle group is non-inferior to outcome in the no treatment group. The Pairwise comparisons of Day 5 healing rate were analyzed using the Cochran-Mantel-Haenszel test. Below is a summary table of this outcome variable:

Percentage of Patients with Complete Ulcer Healing on Day 5
Studies 9E03 and 1U106

Study (duration)	Study site	Amlexanox (A)	Vehicle (V)	No-treatment (N)	Comparison[1]	p-value or LL
9E03 (6/00 – 12/00)	Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)	A vs. V LL for V vs. N[2]	0.026 -5.6%
1U106 (6/02 – 3/03)	Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.7%)	A vs. V LL for V vs. N[2]	0.015 -9.2%

Source: Statistical Reviewer's analysis based on the sponsor's electronic SAS data sets.
[1] Comparison of A vs. V is based on CMH test adjusting for study site; the comparison of V vs. N is based on the lower limit of one-sided 97.5% confidence interval for (vehicle – no-treatment).
[2] LL for V vs. N is the exact lower limit of one-sided 97.5% confidence interval computed using StatXact version 5.

Although both studies have met the test of statistical significance for the percentage of subjects healed on OraDiscA compared to vehicle at Day 5, it is worthwhile to examine the pattern of healing during each of the seven days for purposes of completeness.

Number (%) of Patients with Complete Ulcer Healing Over Time (ITT) – Study 1U106

Time	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.192		
Amlexanox vs. No-treatment	0.179		
Vehicle vs. No-treatment	–2.91%		
Day 4	57 (18.8%)	40 (13.3%)	10 (10.3%)
Comparison[1]			
Amlexanox vs. Vehicle	0.055		
Amlexanox vs. No-treatment	0.050		
Vehicle vs. No-treatment	–4.18%		
Day 5	92 (30.4%)	66 (21.9%)	21 (21.6%)
Comparison[1]			
Amlexanox vs. Vehicle	0.015		
Amlexanox vs. No-treatment	0.093		
Vehicle vs. No-treatment	–9.16%		
Day 6	115 (38.0%)	107 (35.6%)	35 (36.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.535		
Amlexanox vs. No-treatment	0.695		
Vehicle vs. No-treatment	–11.52%		
Day 7	154 (50.8%)	159 (52.8%)	47 (48.5%)
Comparison[1]			
Amlexanox vs. Vehicle	0.560		
Amlexanox vs. No-treatment	0.627		
Vehicle vs. No-treatment	–7.06%		

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 61 and 132-133). Note that the table is intended to observe efficacy trend, otherwise, a multiplicity adjustment would be needed.

[1] The comparison (p-value) of amlexanox vs. vehicle and amlexanox vs. no-treatment each was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the lower limit of one-sided 97.5% confidence interval of the treatment difference (i.e., vehicle – no-treatment).

Note that the effect is the strongest at Day 5 as the sponsor had predicted. At the last day of the trial, Day 7, the difference between the treatment and vehicle groups had actually disappeared and is trending in the wrong direction. Early in the review process, the sponsor was asked about the Day 7 data and explained it in a separate submission to the NDA. They stated that as time progresses, the difference in percentage of subjects healed will lessen between groups due to the natural progression of healing. Without seeing data from the days after Day 7, it is difficult to predict the remainder of the trend. Nonetheless, it is somewhat disconcerting that this difference had disappeared by the time that only half of the subjects had been healed.

Non-inferiority of vehicle to no treatment

The second requirement for a win on the primary outcome variable is that the percentage of healed individuals in the vehicle group is not inferior to the percentage of healed subjects in the no treatment group. This stipulation was included to rule out the possibility that the vehicle makes the ulcer worse and is discussed in FDA's Clinical/Medical Guidance document entitled, Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment (Draft Issued 6/2000). During the 45-day special protocol assessment, the sponsor proposed that non-inferiority would be achieved if the lower limit of the 97.5% confidence interval around the difference between groups is greater than -8%. In the statistical review of this proposal, the reviewer acknowledged that this was acceptable.

As is seen in the summary table at the beginning of this section, the actual value of the confidence interval's lower limit in the pivotal trial was -9.2%. Because this -8% value was proposed by the sponsor, rather than the Agency, and the actual -9.2% value was very close, we must consider whether the value is sufficiently higher to raise a concern about the vehicle disk making the aphthous ulcer worse. It is worthwhile in a situation that is very close such as this, to look at other relevant comparisons, including the results from the Phase 2/3 trial. Because prior studies, including the Phase 2/3 trial had shown a difference of approximately 10% between the vehicle arm and no treatment in the percentage of subjects healed at Day 5, the sponsor used those values for the power calculation. In the pivotal trial, the actual difference on Day 5 was less than 1%. The no treatment arm, while sufficiently powered to detect the difference between active and vehicle, was not able to reach the -8% confidence interval as predicted. However, there is also no evidence to suggest that the vehicle arm had worse efficacy than no treatment (pivotal trial value 27% vs. 26%).

In the Phase 2/3 trial, (see chart at the beginning of this section) the percent of subjects healed for the vehicle arm is 8 percentage points greater than no treatment, and the lower confidence interval for that non-inferiority testing was -5.7%, well less than the 8% value set for the pivotal trial. The Phase 2/3 trial, however, is not viewed as pivotal because of the difference in formulation as was discussed earlier in this review. Although the efficacy of the OraDiscA cannot be considered pivotal due to an additional backing layer which the Agency was concerned would keep the amlexanox in contact with the ulcer longer than the older formulation without the backing, the vehicle does not contain any

amlexanox. Therefore, the effect of the vehicle disk, if negative, would be just as likely to show up in the old formulation as the new, since the adhesive layer is identical in both formulations.

One other piece of information that is also helpful in determining if the vehicle is contributing to making the ulcer worse is to examine the AE profile for local irritation in both the OraDiscA and vehicle groups. The AE profile will be discussed in detail in Section 7.1.5.4 in this review and will show that the percentages are identical in reporting irritation (1.2% for both), and very similar between the two in terms of pain, burning, paresthesia, and reaction NOS. If the vehicle negatively affected the healing of the ulcer, one might observe an increase in local irritation resulting from the placebo.

This additional information from the phase 2/3 trial coupled with the sponsor's very close miss to their own non-inferiority margin is sufficient to conclude that the vehicle has little or no negative impact on efficacy.

Secondary Analysis of Healing – Time to complete healing

The secondary analysis of ulcer size healing is the time to complete healing. Since the sponsor won on percentage of subjects healed on Day 5, a win on this endpoint is not required, but may be helpful in labeling not only for additional comprehension for patients and clinicians but also to be able to compare this to Aphthasol's labeling, which includes it. The data demonstrated a statistically significant difference between the OraDiscA and vehicle (log rank test p=0.034) as well as a statistically significant difference between the OraDiscA and no treatment (log rank test p=.003). However, because the sponsor used median time rather than mean time (as was measured in the Aphthasol trials), it is a not possible to calculate a meaningful mean number of days until healing for each group.

Pain Reduction

The other two secondary outcome variables are measurements of pain reduction. The first is percentage of subjects to achieve pain resolution at Day 5, which is defined as choosing a score of < 5mm on the VAS pain scale. The chart that follows shows not only the comparison of groups at Day 5, but also at the other days of the trial to verify the consistency of this pattern. At every day, including Day 5, the OraDiscA was significantly better than no treatment, but at no day, including Day 5, did OraDiscA demonstrate statistical superiority over the vehicle patch. This is not a surprising finding, as the vehicle patch, by virtue of covering the site and protecting it from insult would be expected to contribute to pain reduction. This confirms that OraDiscA reduced pain, but that amlexanox does not significantly contribute to the pain reduction by itself. The labeling will need to address the fact that the patient may expect pain relief from the entire OraDiscA product, but may not imply or state that the amlexanox alone is producing this effect.

Pain resolution based upon VAS – Cumulative Numbers and Percentages ITT population

Study Day	Amlexanox OraDiscA	Vehicle Patches	No treatment	P value
Day 2, afternoon	23 (7.6%)	16 (5.3%)	1 (1.0%)	0.052
Day 3, afternoon	53 (17.5%)	51 (16.9%)	8 (8.3%)	0.08
Day 4, afternoon	91 (30.0%)	90 (29.9%)	23 (23.7%)	0.44
Day 5, afternoon	134 (44.2%)	132 (43.9%)	30 (30.9%)	0.045
Day 6, afternoon	171 (56.4%)	166 (55.2%)	42 (43.3%)	0.058
Day 7, afternoon	186 (61.4%)	193 (64.1%)	51 (52.6%)	0.12

The other analysis of pain relief, time to complete pain resolution, confirms the above results. In that analysis, the survival analysis for the ITT population demonstrated that the amlexanox treatment group had a statistically significantly shorter median time to pain relief than the no treatment group (5.0 days compared to 6.0 days; log rank p =0.034, Wilcoxon p = 0.016.) The vehicle group was also significantly better than no treatment in pain relief (log rank p = 0.053, Wilcoxon p = 0.041). There was no difference between the amlexanox group and the vehicle group (Both groups had a value of 5.0 days)

Effectiveness for Subgroups – Age, Race and Gender.

Demographically, gender, age and ethnicity data were analyzed by study and by treatment group and are summarized in the table below. Of note is that the groups are balanced for the important demographic characteristics that have the potential to bias the results. Specifically, the mean and median age are nearly identical between all three test groups. The racial breakdown is very similar between all test groups, although Caucasians are slightly underrepresented in the no treatment group, and Hispanics are slightly overrepresented in the no treatment group. Nonetheless, the overall comparison of race produces a p value of 0.60, indicating no significant findings of non-randomness. It must be noted that the percentage of Caucasians (86%) is slightly higher than the overall US population and the African-American population is slightly lower than the overall US population. (2000 Census – 83% Caucasian, 13% Black, 9% Hispanic). Significantly more female than male subjects were enrolled with an almost 3:1 ratio. Although epidemiologic data supports a higher prevalence of aphthous ulcers in females (approximately 55% of aphthous ulcer sufferers are female), the 2:1 ratio of enrollment is higher than predicted. In addition to prevalence, the high ratio reflects the greater propensity of women to seek medical care and to enroll in clinical trials. The mean age for subjects enrolled in the pivotal trial (29.7 years) is lower than the US population (35.8 years)

Subjects were enrolled into the study with 1, 2, or 3 aphthous ulcers. The percentage of each baseline number was adequately randomized between treatment groups. As is expected with recurrent aphthous ulcers, approximately 73% of all subjects had one aphthous ulcer. Approximately 19% presented with two aphthous ulcers, and approximately 8% had three ulcers.

Baseline Characteristics

		Amlexanox OraDiscA	Vehicle Patches	No Treatment	p-value
		N = 303	N = 301	N = 97	
Gender	Female	196 (64.7%)	202 (67.1%)	60 (61.9%)	0.61
	Male	107 (35.3%)	99 (32.9%)	37 (38.1%)	
Age	Mean (S.D.)	29.7 (12.2)	28.9 (12.4)	29.7 (12.4)	0.66
	Median [Range]	26 [12 – 75]	26 [12 – 73]	26 [12 – 68]	
Race	Caucasian	265 (87.5%)	259 (86.0%)	77 (79.4%)	
	Hispanic	21 (6.9%)	22 (7.3%)	11 (11.3%)	
	Black	6 (2.0%)	7 (2.3%)	2 (2.1%)	0.60
	Asian	5 (1.7%)	7 (2.3%)	2 (2.1%)	
	Other/Mixed	6 (2.0%)	6 (2.0%)	5 (5.2%)	
No. of Ulcers Treated Daily During Study					
	1 ulcer	219 (72.3%)	231 (76.7%)	68 (70.1%)	0.63
	2 ulcers	58 (19.1%)	50 (16.6%)	21 (21.6%)	
	3 ulcers	26 (8.6%)	20 (6.6%)	8 (8.2%)	

It should be noted that the studies were not designed to test efficacy within subgroups, but rather to explore trends. There has been no past evidence that patients respond differently to amlexanox based upon age, race or gender. More than 80% of the subjects are Caucasian, and their ulcer healing rates are similar to those based on the overall results. The Hispanic subgroup of approximately 8% showed the same outcome as Caucasians. The Asian and Other subgroups had a small percentage with wider variation, so any conclusions about treatment comparisons are not possible.

In the remainder of this section, the efficacy results by subgroup will be discussed. The following table presents the results from the pivotal trial with stratification by subgroup for age, race, gender, and number of ulcers treated.

Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT)

Study 1U106

Subgroup	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
Age			
Pediatric (12 – 17 years)	11/37 (29.7%)	13/49 (26.5%)	4/12 (33.3%)
Adult (18 – 64 years)	78/263 (29.7%)	53/248 (21.4%)	17/84 (20.2%)
Geriatric (65 and older)	3/3 (100%)	0/4 (0%)	0/1 (0%)
Gender			
Male	30/107 (28.0%)	16/99 (16.2%)	7/37 (18.9%)
Female	62/196 (31.6%)	50/202 (24.8%)	14/60 (23.3%)
Race			
Caucasian	83/265 (31.3%)	55/259 (21.2%)	16/77 (20.8%)
Black	2/6 (33.3%)	2/7 (28.6%)	1/2 (50%)
Hispanic	5/21 (23.8%)	4/22 (18.2%)	1/11 (9.1%)
Asian	0/5 (0%)	3/7 (42.9%)	1/2 (50%)
Other	2/6 (33%)	2/6 (33%)	2/5 (40%)
Number of treated ulcers			
One	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, pages 3-4) and sponsor's electronic SAS data set (LOGIT.xpt).

Men and women had differences in their responses to treatment. Overall, men had larger ulcer sizes at baseline than women, and as expected, not as many men reached total healing by Day 5. Stratification by gender does show consistency in the overall results - in both men and women, the OraDiscA group is superior to the vehicle group.

The results of the one and two ulcers at baseline are consistent with the overall results. However, for those subjects with 3 ulcers at baseline, the trend is that the OraDiscA is inferior to vehicle or no treatment. Because the numbers are very small in this subgroup, interpretation of these results is inconclusive.

For the breakdown by age in the pediatric group (12 – 17 years of age), the results show only a very slight improvement of the OraDiscA group over vehicle, and that the no treatment group fared best. The numbers in this subgroup of pediatrics however, is too small for adequate conclusions. In particular the no treatment group's results of 4/12 improvement would fit perfectly into the overall efficacy pattern with just one less

subject healed (3/12 or 25%). As a follow-up, pediatric efficacy was examined in the phase 2/3 trial as follows:

Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT)

Study 9E03

	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Age			
Pediatric (12 – 17 years)	3/12 (25.0%)	3/11 (27.3%)	3/4 (75.0%)
Adult (18 – 64 years)	71/142 (50.0%)	54/147 (36.7%)	20/76 (26.3%)
Geriatric (65 and older)	2/3 (66.7%)	1/5 (20.0%)	0/1 (0%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, page 6) and electronic SAS data set (Diary_p.xpt).

Once again, the results of the pediatric group do not support the overall trend, but the numbers in this subgroup are too small to draw conclusions about effect. There is no biological hypothesis or supporting evidence that children would respond differently to amlexanox than adults. In addition, pediatric trials are always challenging, particularly in cases where compliance is an issue such as this one where the children would need to be placing new disks four times a day for 7 days. For further discussion of pediatric considerations and recommendations, see Sections 8.3 and 8.4 of this review.

For the geriatric subjects, the numbers are extremely small – a total of 8 geriatric subjects enrolled in the pivotal trial and 9 in the phase 2/3 trial. The trend in both is that the OraDiscA has superior efficacy to the vehicle and the no treatment groups, so although numbers are too small for conclusions, the data trend in the right direction.

Inclusion/Exclusion Criteria Pertinent To the Efficacy Evaluation

The inclusion criteria are appropriate and included male and female subjects ages 12 and above, a history of recurrent minor aphthous ulcers which take 5 days or more to resolve, and at least one ulcer that developed within the last 36 hours prior to screening. Exclusion criteria for the pivotal study include underlying conditions such as diabetes or uncontrolled infection which may interfere with the wound healing, or ulcerative colitis, Crohn's disease, or Behcet's syndrome which also produce oral ulceration. Individuals who wore a denture or orthodontic device that may come in contact with the ulcer were excluded as were individuals who use tobacco products. Individuals who were currently being treated with aspirin, NSAID steroid inhaler, or steroid nasal spray, or retinoids, or immunomodulatory agents were excluded.

The exclusionary conditions are reasonable, and were put into place to avoid confounding variables that may have biased the study results. For example, concomitant anti-inflammatory drug use may likely have a therapeutic effect on aphthous ulcers, making it

difficult to measure the true effect from the amlexanox. Likewise, the presence of diabetes, or the presence of an irritating intraoral appliance would negatively affect the ulcer healing. The impact of smoking on ulcer healing is unclear –data shows that smokers are actually at less risk of developing aphthae than non-smokers. It would be ideal to include these individuals, and distribute them evenly into the various treatment groups, allowing for subgroup analysis. Labeling may need to be crafted to include information about exclusion of some of the diabetics and tobacco users, who encompass a large percentage of the United States population.

6.1.5 Clinical Microbiology

Prior to NDA submission, a request was made to Clinical Microbiology via consult to determine if microbiologic activity was a feature of amlexanox. The clinical microbiologist responded that the medical literature using PubMed in August, 2001 found no references to antimicrobial activity of amlexanox correlated with acceleration of healing of aphthous ulcers. Since OraDiscA has no antimicrobial activity, no further clinical microbiology review was performed.

6.1.6 Efficacy Conclusions

The sponsor has adequately demonstrated that OraDiscA effectively increases the percentage of patients with aphthous ulcers who are healed compared to those who received a vehicle disk. They have also shown that the effect is valid, and was not caused by the vehicle exerting some detrimental effect on the aphthous ulcers.
The effect was also valid in individuals with up to 3 concomitant ulcers. The sponsor was not able to demonstrate that OraDiscA is more effective than vehicle in reducing pain; however, OraDiscA is significantly better than no treatment in reducing pain. The reduction of pain compared to no treatment was most likely due to the reduction of inflammation plus the barrier of the disk relieving pain, although this hypothesis was not specifically tested. The labeling should reflect that OraDiscA is not an analgesic but does help to relieve pain through reducing inflammation.

The pediatric subgroup analysis reveals a trend in the opposite direction in the evaluation of OraDiscA's efficacy. Although there are not large enough numbers to draw statistically sound conclusions, the reversal from the expected trend does not support efficacy in children. Because there is no biological reason to believe that children would not respond to OraDiscA, the trial as designed may have been unable to produce valid results.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred during any of the trials conducted with amlexanox mucoadhesive patch formulation or any other amlexanox formulations. There are no reports in the literature of death linked to amlexanox.

7.1.2 Other Serious Adverse Events

No serious adverse event was reported during any of the trials conducted with amlexanox mucoadhesive patch or during trials of any other amlexanox formulations submitted to this NDA.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

This summary chart includes clinical trials AP-C-1U106, AP-C-2U108, AP-C-9E03, and AP-C-9E02. The first two trials were performed on final formulation of OraDiscA, whereas the latter two were conducted on the earlier formulation.

Subject Withdrawal in AP-C-1U106, AP-C-2U108, AP-C-9E03, and AP-C-9E02

Reason for Withdrawal	Amlexanox Patches (N = 592)	Vehicle Patch (N = 490)	No Treatment (N = 178)
Worsening of Condition	2 (0.3%)	0	0
Adverse Event	4 (0.7%)	5 (1.0%)	0
Subject's Request	13 (2.2%)	4 (0.8%)	10 (5.6%)
Protocol Violation	6 (1.0%)	2 (0.4%)	0
Lost to follow-up	4 (0.7%)	1 (0.2%)	2 (1.1%)
Other Reason	2 (0.3%)	4 (0.8%)	0

Note that nine of the subjects in these four trials withdrew due to adverse events. Subjects who discontinue treatment in association with an adverse event receive special attention in regulations (their CRFs must be submitted) and their analysis is a critical part of the safety evaluation. In the next section of this review, the details regarding the adverse events associated with these subjects will be presented.

7.1.3.2 Adverse events associated with dropouts

Before examining the adverse events associated with dropouts, it must be considered that some of the subjects being evaluated for safety participated in trials that tested the early formulation of OraDiscA and some subjects participated in trials that tested the to-be-

marketed formulation (Refer to the discussion in Section 2.5 of this review for further details on the formulation differences). Although the active ingredient is identical in both formulations, the use of different backing materials raises a question of a potential difference in responses that could affect the safety profile. Therefore, the narrative of the withdrawals provided in this section will be differentiated by formulation group.

Final Formulation Trials
A review of the studies included in this summary chart reveals that of the 592 subjects exposed to amlexanox patches, 409 received final formulation patches. Of these 409, two subjects withdrew from the studies due to adverse events. One of the subjects developed increased redness at the application site and a rough texture of the oral mucosa and tongue starting on Day 4. Treatment was discontinued on Day 5 and the condition resolved by Day 7. The second subject developed nausea on Day 2 and stopped using the patches, whereupon the nausea resolved.

Four subjects in the final formulation trials who were assigned to the vehicle withdrew due to reported adverse events. One subject withdrew due to reported nausea after the first day of use, which resolved after discontinuation. Another subject reported lip swelling, nausea, intermittent headache and discomfort at the application site on Day 2 - the events resolved the same day, after discontinuation of the product. A third subject on final formulation vehicle developed itching on her face, eyes, ears and throat that began on Day 1; she discontinued the study drug and the event resolved later that day. The fourth subject reported pain and swelling of the lower lip close to the ulcer site. She was withdrawn from the study, and the pain and swelling resolved when the ulcers had healed on Day 11.

Early Formulation Trials
Two of the 194 subjects who received the early formulation withdrew due to adverse events. One subject had a 20-minute episode of increased heart rate and light-headedness after one day of treatment and stopped using the product. The second subject withdrew on Day 5 due to severe pain at the application site.

In the early formulation vehicle group, one subject withdrew from the study on the third day due to nausea. The nausea abated later on the third day.

The fact that these adverse events associated with dropouts are few, mild, and evenly distributed between the test group and the placebo is a good indication that there was not a pattern of discontinuation of use of the product resulting from adverse events. In terms of causality, it is possible that both the vehicle and the active disk are capable of causing localized irritation, nausea, or sensitization as reported in these dropouts. A full analysis of all adverse events reported in these trials will be discussed later in this review.

7.1.3.3 Other significant adverse events

Eight adverse events that occurred in the clinical trials did not lead to discontinuation but are considered significant and are described in this section. Significant adverse events

are defined by ICH as marked hematological, laboratory, or other abnormalities not meeting the definition of serious. Seven of the events occurred in the trials that used the new formulation and the other in a trial using the old formulation. In the trial using the old formulation, one subject assigned to the amlexanox patch experienced a rash on Day 3 on both cheeks. The examiner recorded light erythema, but no swelling or other evidence of inflammation. The subject declined to return to the study center for further investigation.

Of the seven subjects enrolled in final formulation trials, four who reported events were assigned to the amlexanox group, and three to the vehicle group. The subjects on active drug reported the following:

1. One subject recorded in her diary tongue soreness beginning on Day 5 and vesicles starting on Day 7. She did not mention these events to the investigators, and the investigator did not observe the events during visit examinations. The subject completed the 28-day study.
2. Another subject reported mild burning and mild redness at the patch application site, beginning on Day 26. The subject completed the 28-day trial and returned on Day 30 at which time the reactions had resolved.
3. A third subject reported redness and irritation at the application site after three days of treatment. The investigator noted that the aphthous ulcer had increased in size. The patient completed this 7-day study, although the investigator noted that on Day 7 the ulcer was still not improved. All events resolved on Day 10.
4. A subject reported mild bleeding at the application site on Day 5, which resolved on Day 6. The subject completed the 7-day trial.

Vehicle Disks:

1. One subject reported mild cheek swelling on Day 2 that resolved on Day 4; the subject completed the seven days of the study.
2. Another subject reported mild irritation and edema at the application site on Day 3, which resolved on Day 4. The subject completed the 7-day study.
3. A third subject reported an increase in size and pain related to the aphthous ulcer on Day 3. The subject completed the trial.

Laboratory testing was performed in one study only (AP-C-2U108); the tests were performed prior to the first application of amlexanox patch and during the last study visit after 28 days of treatments. None of the laboratory testing revealed marked hematological or other lab abnormalities that would warrant discussion in this section. In Section 7.1.7 of this review, laboratory testing will be described in full and any potential abnormalities discussed.

7.1.4 Other Search Strategies

There were no safety signals that arose from the sponsor-conducted studies that required construction of any algorithm involving combinations of clinical findings as a marker for

a particular toxicity. No pharmacologically-related drugs produced signals of such concerns. However, a concern about potential aspiration of the disk was raised by the Agency during the EOP2 meeting. In Section 7.1.12 of this review, the results of the sponsor's measure of erosion time and review of past safety data will be discussed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

During all of the clinical trials, the Investigator questioned subjects at every visit about adverse events using an open question, and was instructed not to influence the subjects' answers. Subjects were also questioned at each visit to assess the reaction to patch application. The following two questions were asked at each visit:

> "Have you noticed any change in your health since the last visit?"
> "Did you experience any pain or discomfort when using the patches?"

All adverse events, either reported verbally by the patient or observed by the investigator, were transcribed onto the Case Report Form. On that form, events were reported as either "application site reactions" or general events.

An Adverse Event Form was completed for any subject starting a new concomitant therapy, other than vitamins, after enrollment into the study. A change in a concomitant therapy resulting from a change in the disease or medical condition for which the therapy is being taken was fully documented on the Concomitant Medication Form as well as by completion of an Adverse Event Form, when appropriate.

When an adverse event persisted at the end of the study, the Investigator ensured a follow-up of the subject until the Investigator/Sponsor agreed the event was satisfactorily resolved.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor grouped closely related investigator or subject reported terms using the MedDRA dictionary of preferred terms. One weakness of the dictionary is that there may be many related terms that may be used to describe an event. Though this "granularity" can result in missing a signal, this was not an issue in this case. From the pooled safety data from all clinical trials, the most commonly reported AE is application site reactions. Of 81 total application site reactions the MedDRA dictionary breakdown showed 39 for pain, 7 for irritation, 21 for burning, 8 for paresthesia, all of which matched the reporting on site. Reports from the six subjects that are listed in the table as application site reaction NOS is a result of the subjects not being more specific to the reporter.

7.1.5.3 Incidence of common adverse events

Adverse Events Reported from Randomized, Vehicle-Controlled Trials

	Amlexanox	Vehicle	No treatment
Application Site Reactions	N = 486	N = 490	N = 178
Pain	36 (7.4)	36 (7.3)	0
Burning	18 (3.7)	15 (3.1)	0
Paresthesia	8 (1.6)	12 (2.4)	0
Irritation	5 (1.0)	6 (1.2)	0
Dryness	0	2 (0.4)	
Reaction NOS	1 (0.2)	14 (2.9)	0
Gastrointestinal Disorders			
Nausea	11 (2.3)	14 (2.9)	0
Mouth Ulceration (i.e., new aphthous ulcers)	8 (1.6)	17 (3.5)	8 (1.7)
Sore Throat NOS	5 (1.0)	6 (1.2)	1 (0.6)
Vomiting NOS	4 (0.8)	1 (0.2)	0
Diarrhea NOS	2 (0.4)	3 (0.6)	0
Nervous System Disorders			
Headache NOS	22 (4.5)	18 (3.7)	2 (1.1)
Taste Disturbance	2 (0.4)	5 (1.0)	0
Fatigue	3 (0.6)	0	0

This table contains data from only the placebo-controlled trials in order to best estimate comparative incidences for common adverse events. Although eliminating the open label safety trial yields a smaller portion of the overall database, the ability to compare rates on drug with a control is an advantage. The subset of trials in the Phase 2 and 3 vehicle-controlled study databases provide the best estimate of incidence rates.

Note that this table presents not only the OraDiscA and its vehicle, but also the no-treatment arm. Although trying to elicit application site reactions when there is no application of either drug or placebo may appear meaningless, note that sore throat and headache were each reported several times. Underreporting of AEs is expected, as subjects who know they are receiving no treatment are less likely to report episodes of headache, nausea, etc. On the other hand, the vehicle group is just as likely as treatment group to report systemic AE's that they experience. None of the common adverse events listed in this table were identified as serious.

The results of this table show a remarkable similarity in reported adverse events between OraDiscA and its vehicle. The only differences in adverse events between the OraDiscA and vehicle are application site reaction NOS and mouth ulceration. Due to the not-otherwise-specified grouping, no further information is available to determine if a more specific type of irritation can be identified. The reported incidence of new aphthous ulcers is much higher in the vehicle than either the OraDiscA group or no treatment group, which may suggest that amlexanox has some sort of preventive effect on new ulcer development. However, the numbers are too small to draw any conclusions.

A revised table that includes all of the studies in which safety was examined will form the basis for the ADR table in labeling in the package insert. That table appears in the next section of this review.

7.1.5.4 Common adverse event tables

The table presented in this section includes not only the vehicle and no-treatment controlled trials, but also the open-label safety study. It is a complete recording of adverse events from all subjects who participated in a trial with the final formulation of OraDiscA. This table includes reactions that occurred at a rate of 1% or more. The application site reactions are likely due to the disk itself, so it is important for the prescriber and patient to see that application site reactions may be expected, but are not worsened by the amlexanox itself. Although the no treatment arm does not add any information to the section on application site reactions, it does give background incidence on the development of new aphthous ulcers, sore throat and headache.

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)	0
Burning	11 (2.7)	9 (3.0)	0
Irritation	6 (1.5)	6 (2.0)	0
Reaction NOS	5 (1.2)	0 (0)	0
Paresthesia	3 (0.7)	4 (1.3)	0
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

Note that the additional subjects in this table as compared to the table in section 7.1.5.3 did not significantly change the relationship of adverse events.

7.1.5.5 Identifying common and drug-related adverse events

Application site reactions were the most common AE's and occurred with nearly equal incidence in the treatment and vehicle groups. There were no reports of application site reactions in the no-treatment group, because nothing was applied. It is difficult to determine whether the application site reactions in the amlexanox and vehicle groups are caused by the presence of a disk, or the presence of the aphthous ulcers which may cause

pain, burning, irritation, and paresthesia. However, because the incidence in the amlexanox and vehicle groups is similar it does not appear that the amlexanox itself is contributing to these local reactions to any significant extent.

As the table shows, adverse events in the Gastrointestinal, Investigations and Nervous System SOCs also were reported by at least 1% of patients. Nausea is an event which can result from the taste of the disk, the physical presence of a disk in the mouth, or possibly (but not likely based on the similar numbers of AE reports) from the amlexanox itself. There were no reports of nausea in the no treatment group.

As noted in the previous section, the reported incidence of new aphthous ulcers, (mouth ulceration) is much higher in the vehicle than either the OraDiscA group or no treatment group, which may suggest that amlexanox has some sort of preventive effect on new ulcer development. Sore throat is numerically greater in the active and vehicle groups, but the numbers are small.

Abnormal liver function tests were reported in 2% of the patients in the active arm, and will be discussed in section 7.1.7, laboratory findings.

Headache is much more commonly reported in the active and vehicle groups than in the no treatment group. Bad taste, which occurred with both the test and placebo disk most likely comes from the disk itself and is likely product-related, through not necessarily amlexanox (substance only) related.

To detect significant relationships with hypothesis-testing methods, any reasonable correction for multiplicity would make a "finding" almost impossible and studies are almost invariably underpowered for statistically valid detection of small differences. However, because we cannot rule out the amlexanox or the disk itself as causing any of these events, the Agency concludes that there may be a causal relationship between the OraDiscA and application site reactions, nausea, headache, and sore throat.

7.1.5.6 Additional analyses and explorations

In some cases, it is helpful to perform a more in-depth analysis of adverse events that seem clearly drug-related. For example, exploration for dose dependency, time to onset of AE's, adaptation for common, troublesome events such as somnolence or nausea, demographic interactions, or of drug-disease and drug-drug interactions can be performed. If necessary, selective exploration of individual cases can better characterize the events. In the case of OraDiscA, there is only one dose and one dosing regimen that is used, which rules out this exploration. The lack of severity and relatively low incidence of all adverse events other than application site irritation do not warrant further scrutiny of these AE's. Liver function testing was only performed during the 28-day safety study on subjects using the OraDiscA, so there is no placebo group to compare. The abnormal liver function results were discovered in two subjects of the total users of OraDiscA, and will be examined in further detail in section 7.1.7 to determine if further testing is required.

7.1.6 Less Common Adverse Events

In general, a fairly large database is needed to evaluate less common adverse events. To identify relatively rare events of significant concern, data from the entire Phase 2-3 database as well as data from the open label trial is included. The following listing grouped by system organ class includes adverse events reported with an incidence of between 0% and 0.8%:

Gastrointestinal: Vomiting, diarrhea, abdominal pain, chapped lips, glossodynia, sensitivity of teeth, tongue dry, dry mouth, oral pain, tooth disorder NOS
Skin and subcutaneous tissue disorders: Dermatitis NOS, pruritus NOS
Eye disorders: Eye pain
General disorders: Pyrexia , pain in face
Musculoskeletal, connective tissue and bone disorders: Pain in jaw
Ear and labyrinth disorders: Earache
Respiratory, thoracic and mediastinal disorders: Sneezing

An examination of the numbers and distribution of these AE's between OraDiscA, vehicle, and no-treatment groups in which they appear does not warrant further investigation at this time.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The studies conducted for efficacy of OraDiscA were of seven-days duration. Laboratory testing was not performed during these studies. In the 28-day open-label study, which was conducted to fulfill long-term safety requirements for approval (AP-C-2U108), laboratory tests as listed below were performed prior to the first application of the amlexanox patch and during the last study visit after 28 days of treatments. Although it is usually preferable to perform the tests on the active and vehicle groups in a clinical trial, the testing of the subjects prior to administration of the drug, and after 28 days of daily use uses the subjects as their own controls to examine any treatment-emergent changes in laboratory values. The labeled duration of use per aphthous ulcer episode is 7 days; by conducting this trial with four back-to-back cycles of treatment, the sponsor has simulated 5-6 months of OraDiscA use. This is adequate, as actual use for recurrent ulcers would have several weeks of no treatment between each cycle of OraDiscA. Any effects on laboratory values should be more readily evident after 28 consecutive days of drug use than with 28 days use extended over six months.

The following laboratory tests were performed:

Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.

Serum Chemistry: glucose, sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, uric acid, phosphorus, serum adjusted calcium, cholesterol, triglycerides, protein, albumin, globulin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, lactic dehydrogenase (LDH), bicarbonate, gamma-glutamyl transferase (GGT).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. Because laboratory testing was performed only in the open label trial, it is not possible to compare any changes from baseline to subjects who received a placebo or no treatment.

7.1.7.3 Standard analyses and explorations of laboratory data

In situations where there is suspicion of a negative impact of the drug on patient laboratory values, three standard approaches to the analysis of laboratory data are often used; the first two analyses are based on comparative trial data, and the third analysis should focus on all patients in the Phase 2-3 experience. Prior exploration of amlexanox's effect on laboratory values in Aphthasol and in amlexanox tablets has not demonstrated any abnormalities. In the case of OraDiscA, there is no comparative data available, as laboratory values were only collected during the uncontrolled open-label study. In section 7.1.7.5, the two subjects who were found to have elevated liver enzymes are discussed to rule out causality of amlexanox to these events. No other laboratory findings required further analyses.

7.1.7.4 Additional analyses and explorations

There is no signal from the summary data to warrant additional analyses for dose dependency, time dependency, or drug-demographic, drug-disease, and drug-drug interactions. Further discussion of the two subjects with treatment-emergent abnormalities in liver function tests, follows in section 7.1.7.5.

7.1.7.5 Special assessments

Two subjects of the 106 who participated in the 28-day open label safety trial of amlexanox patches (study AP-C-2U108) had clinically significant laboratory abnormalities in liver function tests reported. Hepatotoxicity has been an important cause of market withdrawal since the 1950s and deserves a special assessment in this section.

These subjects were measured at the beginning of the trial and at the end. The elevated laboratory values in both subjects were deemed by the investigators to be not related to study medication, but likely due to undiagnosed gallbladder disease and concomitant medication treatment respectively, as described below:

Elevated laboratory values in subject 175-054

Subject #		Normal	Baseline	Day 38
175-054	Alkaline Phosp	37 – 147	169	332
	AST	5 – 45	42	55
	ALT	1 – 55	53	114
	GGTP	1 – 50	123	173

Subject #175-054 had mildly elevated levels of Alkaline Phosphatase and GGTP at screening, which the investigator identified as transient and resulting from ingestion of two tablets of naproxen sodium the evening prior to the screening visit. Although this mild elevation did not exclude the subject from being enrolled, the subject dropped out of the study at Day 3. The subject returned on Day 38 for final laboratory testing and notified the site that a diagnosis of gallbladder stones was made by the subject's physician on Day 59.

Elevated laboratory values in subject 184-064

Subject #		Normal	Baseline	Day 35	Day 45
184-064	Alkaline Phosp	37 – 147	117	165	133
	ALT	1 – 55	18	181	22
	GGTP	1 – 50	17	108	49

Subject 184-064 completed study treatment on Day 31 as planned. On Day 35, alkaline Phosphatase, ALT and GGTP were all elevated. Upon questioning, the subject stated that he had developed a viral infection on Day 32 and was treated with promethazine hydrochloride. On a follow-up visit on Day 45, levels had returned to normal. The investigator concluded that by Day 35, the OraDiscA should not have been responsible for the elevated enzymes, but the temporal association with the promethazine fits the profile. The Agency concurs that amlexanox is not likely to have been the cause of the transient elevation.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured at baseline only during the 28-day safety study for the purposes of determining eligibility for the study. There was no vital sign assessment during the phase 3 trial. Therefore, no analyses were conducted on vital signs or physical findings. Based upon the prior approval of Aphthasol paste, 16-year systemic use of amlexanox in Europe at 10 – 20 times the dose, and the minimal absorption of amlexanox, vital sign monitoring during the trial was not deemed to be necessary.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.8.3 Standard analyses and explorations of vital signs data

No standard analyses and explorations of vital signs data were performed. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data were performed. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

There were no ECGs obtained during any of the studies, either at baseline or during the course of the study. This drug is a topical drug that demonstrates virtually no systemic absorption through the oral mucosa. The only systemic exposure is through swallowing the disk as it slowly dissolves. Based upon the prior approval of Aphthasol cream, which resulted in swallowing the same amount of active ingredient, as well as a 16-year history of systemic use of Amlexanox in Europe at 10 – 20 times the dose for a chronic indication, its cardiac safety has been well established.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and explorations of ECG testing were performed. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.9.4 Additional analyses and explorations

No additional analyses of ECG data were performed. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.10 Immunogenicity

Although amlexanox has been shown to have antiallergenic activity in various models of Type I to Type IV allergic reactions when provided by systemic administration, many cases of contact dermatitis have been reported with certain of the topical forms of amlexanox. In Japan, there is a marketed ophthalmic solution containing 0.25% amlexanox. Of the — million patients who used amlexanox ophthalmic solutions, 125 cases of contact dermatitis associated with the ophthalmic solution were reported to the manufacturer. The dermatitis occurred primarily around the eyes and it was concluded that amlexanox was a sensitizer when brought into direct contact with the skin around the eyes. Similarly, one study with a 1% gel formulation of Amlexanox being tested in

patients with oral lichen planus has resulted in a high degree of sensitization, and skin testing suggested an immune-mediated hypersensitivity reaction. Repeated patch-application tests conducted with an investigation of a 2.5% and 5.0% cream formulation also resulted in a high degree of hypersensitivity.

Therefore, prior to approval of amlexanox paste in the U.S., a repeated-injury patch test study was conducted in 200 healthy volunteers. In addition, a long-term safety study was conducted in 100 patients with aphthous ulcers for 28 days. No sensitization reactions were observed in either study. Post-marketing surveillance of Aphthasol in the U.S. has included only 16 reports of allergic reactions to the oral cavity or face between 1995 and 2001. During that period of time, [ ] tubes of Aphthasol were dispensed. In addition, the oral amlexanox tablets in Japan have reported very few skin eruptions, leading to speculation that systemic administration of amlexanox results in a low incidence of sensitization.

In conclusion, the allergenicity of amlexanox appears to be primarily a function of the formulation – Amlexanox oral tablets, amlexanox 5% paste, and amlexanox 2 mg oral patches have a low incidence of hypersensitivity reactions, whereas ophthalmic solutions, creams and gels have a much higher incidence of hypersensitivity. Since the potential exists for cases of hypersensitivity with OraDiscA once in widespread use, a statement about discontinuing use if hypersensitivity develops is warranted.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under the IND for OraDiscA or Aphthasol. There were no data or literature submitted to this NDA on the topic.

7.1.12 Special Safety Studies

In some cases, special studies are warranted for concerns that arise such as QT interval abnormalities, or drugs that are intended to demonstrating a safety advantage over other therapies. Although this is not the case for OraDiscA, one safety concern unique to a mucoadhesive patch that the sponsor addressed was the risk of aspiration, since the patch is applied to the oral mucosa and designed to dissolve slowly over time. In fact, one of the reasons that the sponsor changed formulations between Phase 2 and Phase 3 of development was to eliminate a [ ] backing and substitute a cellulose-based one. The sponsor was concerned that if some patients did not understand that the [ ] backing was to be removed before placement, there would be a danger of swallowing or aspirating the [ ] The sponsor addressed the concern about aspiration in two ways. They monitored the clinical trials of 603 subjects using OraDiscA as well as an additional 409 subjects using a vehicle patch, and found no reports of accidental aspiration or detrimental swallowing of the patches. In addition, the sponsor conducted a pharmacokinetics study in which the erosion time of the patch was specifically measured and the subjects queried about particulate dissolution. The patch eroded within 1 – 2 hours, and subjects did not have problems with the OraDiscA breaking into large particles. In spite of the apparent safety in these clinical trials, the sponsor decided to

include in the label a statement advising patients against using the disk too close to bedtime to prevent aspiration while sleeping.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Amlexanox paste has been used for the same indication in the US for seven years, and amlexanox has been taken internally in Japan since 1987 for allergic rhinitis. There have been no signals of abuse potential or withdrawal symptoms. Therefore, no studies were designed to assess these issues. No concerns about abuse potential have arisen from the studies conducted for this NDA. The Agency concurs that there is no need to examine this area any further at this time.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies in humans of the effects of drugs on reproduction or pregnancy were performed. Similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development was identified. 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 a significant effect on peri- or postnatal development of rat fetuses. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Therefore, OraDiscA is recommended for Pregnancy Category B.

7.1.15 Assessment of Effect on Growth

This drug was tested in children age 12 and older and is labeled as such. The efficacy trials were of seven-days duration, and the long-term safety study was 28 days. There was no concern either prior to the conduct of these clinical trials or during the review of this NDA that topical amlexanox has an effect on growth or development. Data were not collected to examine this parameter.

7.1.16 Overdose Experience

There are no reports of overdosage. Ingestion of 20 patches (proposed packaging for one prescription) would result in systemic exposure well below the maximum nontoxic dose of amlexanox in animals, as well as below the maximum daily oral dose of 50 mg of amlexanox tablets t.i.d. used to treat asthma in other parts of the World. Gastrointestinal upset such as nausea, vomiting, and diarrhea could result from an overdose.

7.1.17 Postmarketing Experience

OraDiscA has not been marketed in the U.S. or any other country. However, amlexanox has been marketed in the U.S. since 1996 as Aphthasol 5% paste, and has been marketed in Japan as 50-mg oral tablets. Examination of postmarketing experience for both of these is helpful for a complete review of OraDiscA.

The post-marketing experience with Aphthasol in the U.S. has included reports of 16 cases that can potentially be characterized as hypersensitivity reactions (oral cavity or face) between October 1995 and June 2001. A total of [ ] tubes of Aphthasol were sold by pharmacists during that time period. Amlexanox tablets have been marketed in Japan since 1987 and postmarketing surveys have included reports of dermal effects such as rashes, urticaria and pruritus; central nervous system effect such as headaches, dizziness, sleepiness and insomnia; gastrointestinal effects such as vomiting, nausea, and diarrhea, and increased liver enzymes. The reported abnormalities of liver function testing occurred in patients receiving chronic doses of amlexanox at 75 – 150 mg/day for 15 – 84 days of treatment. The changes were asymptomatic and returned to normal levels following discontinuation of treatment. The incidence of elevated liver enzymes occurred in 0.2% of patients who were tested in the post-marketing surveys of amlexanox tablets.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 summarizes the clinical trials that were submitted to this NDA to support both safety and efficacy. Although only three of them contained data that was used in the evaluation of efficacy, all of these trials collected safety data which were evaluated for the purposes of establishing safety of OraDiscA. The phase 2/3 and phase 3 pivotal trials examined 460 subjects using OraDiscA for seven days and the open label study evaluated 106 subjects using OraDiscA for 28 days. As was discussed in Section 6.1.4, there was adequate representation of individuals from the major U.S. racial groups, men and women, and all age groups over 12.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table that lists all clinical trials and summarizes the design features and number of subjects in each trial. The subjects included in the safety evaluation were enrolled in five clinical trials. Three of the trials were vehicle-controlled, efficacy and safety trials, based on seven days of treatment or less, and four-times-daily applications. This corresponds to treatment during a single episode of an aphthous ulcer. In the fourth study, the safety of repeat treatment with OraDiscA was evaluated using 106 subjects with aphthous ulcers. The subjects were enrolled in the long-term safety clinical trials and asked to treat one or two ulcers with OraDiscA four times a day for 28 consecutive days. The sponsor did this to simulate exposure that is equivalent to four to five consecutive treatment courses. The fifth study was a phase 1 pharmacokinetics study in healthy individuals that primarily determined if there were any early signs of safety problems before enrolling aphthous ulcer patients.

The 28-day safety trial and the pivotal seven-day safety and efficacy trials were conducted with the final formulation of OraDiscA, whereas the other two trials were conducted with the earlier formulation. As has been discussed earlier in this review, although there were some concerns about how the change in formulation might affect the efficacy results, the safety data from the two formulations should be comparable.

A total of 409 subjects with aphthous ulcers were exposed to the final formulation and 309 to its vehicle patch. An additional 194 subjects with aphthous ulcers were exposed to the earlier formulation and 189 to the vehicle formulation of the earlier formulation. Therefore, the total number of subjects included in the safety database is 603 (409 + 194) subjects on active amlexanox patch.

7.2.1.2 Demographics

Refer to the table in Section 6.1.4 which contains the demographic breakdown of subjects. In all studies, significantly more female than male subjects were enrolled with an almost 2:1 ratio. The relative proportion of women versus men among studies and treatment-groups ranged from 73% vs. 27% (vehicle group in AP-C-9E02) to 57% vs. 43% (vehicle group in AP-C-9E03). This gender difference is due to the fact that more women are affected by recurrent minor ulcers plus women in general are more likely to volunteer for clinical trials. In spite of the higher percentage of female enrollees, there are sufficient men to examine gender differences in safety or efficacy. In terms of racial enrollment, it must be noted that the percentage of Caucasians (86%) is slightly higher than in the overall U.S. population and the African-American population is slightly lower than in the overall U.S. population. (2000 Census – 83% Caucasian, 13% Black, 9% Hispanic). Although there were too few enrollees from minority races to perform statistical testing, those subjects were examined for trends in both safety and efficacy evaluations. The mean age for subjects enrolled in the pivotal trial (29.7 years) is lower than the US population (35.8 years). Subjects were enrolled from the age of 12 with no upper limit. Due to a lack of formal recruiting of geriatric patients, their numbers were very small, and although no conclusions could be made, the safety and efficacy were similar in trend to the other adults.

7.2.1.3 Extent of exposure (dose/duration)

There was only one dosing regimen used for all trials – one patch four times per day. Because this dosing was established in the Aphthasol product, the sponsor did not wish to explore other strengths or dosing frequency. For the purposes of testing, a seven-day dosing, which is the same dosage and administration as proposed for the label, was used in all of the trials with the exception of the open label trial. That trial was conducted for 28 days, which approximates four cycles of treatment to simulate chronic use.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Secondary source data are (1) data derived from studies not conducted under the applicant's IND and for which CRFs and full study reports are not available, or studies so poorly conducted (e.g., poor ascertainment for adverse events) that they cannot be reasonably included in the Primary Source Database, (2) postmarketing data, and (3) literature reports on studies not conducted under the IND. As has been described in Section 7.1.17 of this review, amlexanox has been marketed in the U.S. since 1997 as Aphthasol 5% paste, and is marketed in Japan as 50-mg oral tablets.

Because Aphthasol was approved under an NDA, reporting of post-marketing experience is mandated and all reports have been reviewed. A total of [ ] tubes of Aphthasol were sold during that time period, which suggests significant exposure. Amlexanox tablets have been marketed in Japan since 1987 and in addition to spontaneous reporting, formal postmarketing surveys have been conducted. Because of chronic doses of 75 – 150 mg amlexanox/day, liver enzyme activity, in particular, was monitored.

7.2.2.2 Postmarketing experience

Although OraDiscA has never been marketed either in the United States or elsewhere, other amlexanox-containing products including Aphthasol and amlexanox 50-mg tablets have. Postmarketing data for Aphthasol are available through the FDA's Adverse Events Reporting System (AERS), and have been evaluated and included in the relevant sections of this review. Data and published literature regarding the amlexanox tablets, which are not marketed in the United States, are not as widely available, but have also been included in the pertinent sections of this review. Important events from these other products have been described in appropriate sections (e.g., 7.1.1 and 7.1.2, Deaths and Other Serious Events; 7.1.16, Overdose Experience).

7.2.2.3 Literature

Most of the literature submitted to this NDA consists of published toxicology studies and papers discussing the etiology and epidemiology of recurrent aphthous ulcers. In terms of referencing studies on other forms of amlexanox, the sponsor owns the data from Aphthasol, so instead of published literature, the actual study reports and tables were provided.

For completeness, literature searches were conducted by the reviewer to ascertain that no published reports that might raise safety or efficacy issues were omitted from the NDA.

7.2.3 Adequacy of Overall Clinical Experience

A total of 592 subjects were exposed to OraDiscA in all studies. Of these, 493 completed studies in which they used OraDiscA for seven days and 99 subjects completed studies in which they used OraDiscA for 28 days. The trials which were of seven days duration tested the drug for the recommended duration of application for each aphthous ulcer

incident. Only the open-label safety study was long enough to simulate six months of chronic use experience. Since many aphthous ulcer sufferers develop ulcers on a fairly regular basis, it is not unusual to be treated for a seven-day cycle 10-12 times per year. This qualifies as a chronic use drug. As recommend by the ICH guidance on extent and duration of exposure, long-term safety data should be collected on a sufficient number of subjects for a sufficient duration to assess safety for chronic use drugs. In the open-label trial, 99 subjects completed the 28-day study. As will be discussed further in Section 7.2.8, this smaller than recommended number must be balanced against the very positive safety profile gathered from the open-label use study as well as the profile from the 493 subjects using OraDiscA in the normal seven-day cycle, 303 of whom received OraDiscA in the pivotal trial. In addition to that, the sponsor has submitted all safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use.

Adequate representation of men and women, individuals of Caucasian, African American and Hispanic background, and adolescents from 12 – 17 were represented. Patients who were excluded from the study such as diabetics and tobacco users, do not limit the relevance of safety assessment, although their exclusion does leave concerns about generalizability of efficacy and are addressed in the proposed labeling. There were no class effects evaluated, other than potential for local irritation from the class of topical drug products. Refer to Section 8.4 for a full discussion of the adequacy of pediatric enrollment and outcome.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the preclinical program conducted prior to Aphthasol's approval and the seven years of human experience for Aphthasol, no additional preclinical testing or in vitro testing was necessary.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of study subjects presented in this submission, including efforts to monitor laboratory parameters, vital signs, and efforts to elicit adverse event data is adequate. Because of the extensive safety testing of amlexanox during the approval process for Aphthasol, it was not necessary to repeat most of this testing for OraDiscA. Vital signs and ECG data were not collected during the clinical trials, but there was no reason to require this for a topical drug with a safe history. Laboratory parameters were monitored during one of the trials at baseline and during the final visit. Although there was no control group for comparison, the subjects were compared to their baseline values. There were very few shifts in lab values, and for those few, no cause for concern for patient safety was identified. The adequacy of specific testing intended to assess certain expected or observed events is discussed under subheading 7.2.7.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review summarizes the clinical pharmacology for amlexanox. Although the exact mechanism of action of the drug is unknown, metabolism and excretion is

sufficiently understood to ease concern about safety problems in patients with impaired excretory or metabolic function, as well as problems resulting from drug-drug interactions.

Both in vitro and in vivo testing carried out by the sponsor were adequate to identify the following: 1) the enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins 2) the effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds and 3) the major potential safety consequences of drug-drug interactions. None of these issues raised concerns that require further testing or specific labeling for OraDiscA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has adequately gathered information, reviewed data from related products, and analyzed information to detect specific adverse events that are potentially problematic and might be expected with a drug of any class (e.g., QT prolongation or hepatotoxicity) or that are predicted on the basis of the drug class. Because of a concern about potential sensitization, the sponsor conducted additional testing, and because of the sponsor's concern about aspiration of the disk, additional testing was conducted and specific labeling recommended.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data submitted for conducting the safety review were sufficient to make the judgment that OraDiscA is safe to proceed to market. As has been discussed throughout the safety portion of this review, information obtained from earlier formulations of amlexanox was used as evidence of safety for the drug substance, amlexanox. Adequate analysis and interpretation of the safety results, including laboratory values, adverse event reporting, and pharmacokinetics have made for a thorough examination of OraDiscA.

Fewer than the ideal number of subjects (100) were enrolled to test chronic use of the drug. This smaller than ideal number is balanced against the very positive safety profile gathered from the chronic use study as well as the safety profile from the 500 subjects on Amlexanox in the normal seven-day cycle. In addition, the sponsor has submitted all safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use. Given that nothing surfaced as a potential safety issue from the wide range of safety data that were submitted, the totality of the safety evidence is sufficient to support the conclusion that OraDiscA is safe.

7.2.9 Additional Submissions, Including Safety Update

The only additional safety submission to this NDA after the initial submission was the 4-month safety update, which was received on August 23, 2004. Since no clinical trials

have been preformed between December 2003 when the original NDA was submitted and July 30, 2004, there is no additional clinical trial safety information to report regarding the OraDiscA drug product. However, the report of a clinical pharmacology safety study is included in this update, which was conducted to evaluate the effects of amlexanox on CYP450 19, 1A2, 2C19, 2D6 and 3A4 and amlexanox binding to the hERG potassium channel protein. The conclusion is that amlexanox did not significantly affect any of the six cytochrome P450 enzymes tested in this study, or the hERG potassium channel. This information is presented in the Clinical Pharmacology section of this review (Section 5).

There are no reports of important changes in Aphthasol labeling or foreign labeling.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The only adverse events that are potentially treatment-related are local irritation at the placement site of the OraDiscA, and possibly nausea, sore throat and headache. The incidence of these events is fairly low at the highest being pain at 7%. Background pain from an aphthous ulcer was not measured, but is likely to be at least that high as well. None of the events reported were serious in nature. Inclusion in the label of a chart that provides this information is sufficient.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety data were examined both on an individual study basis and as pooled data, depending upon the intent of the data review. In order to estimate the incidence of adverse events in clinical trials, the data were first tabulated, using only the controlled clinical trials. The subjects were blinded and therefore, a comparison to vehicle provides a fairly realistic picture of how much of an adverse effect is related to the study medication. The use of an open label study or other unblinded or uncontrolled trials could bias the results.

On the other hand, pooling all of the safety data increases the sample size and increases the chance of seeing lower frequency events, which can be difficult to detect and may not occur in some studies. Pooling can also provide a larger database that will permit explorations of possible drug-demographic or drug-disease interactions in population subgroups. In the safety review, the source of the data has been identified in each section.

7.4.1.2 Combining data

As described in 7.4.1.1, safety data were pooled to increase the likelihood of uncovering adverse events that occur with a low frequency. The pooling procedure consisted of

combining the numerator events and denominators for the selected studies. Although more formal weighting methods can be used (e.g., weighting studies on the basis of study size or inversely to their variance), this was not deemed necessary for OraDiscA.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

There is only one dose of OraDiscA proposed.

7.4.2.2 Explorations for time dependency for adverse findings

The recommended use for OraDiscA is seven days for each aphthous ulcer occurrence. All of the clinical trials except for the open-label trial were of seven days duration. The open-label study of 28 consecutive days had a slightly higher incidence of adverse events, which is expected due to the much greater exposure time. Since the dosing for each aphthous ulcer outbreak is seven days, the results from the seven-day studies are more typical of actual use. Nonetheless, the 28-day safety data is included in the pooled safety data results.

7.4.2.3 Explorations for drug-demographic interactions

The effectiveness and safety of OraDiscA was explored to the extent possible in race, age, and gender subgroups. Although there is some concern about effectiveness in children between the ages of 12 and 17, there were no safety concerns in any of these groups.

7.4.2.4 Explorations for drug-disease interactions

There was no evidence of drug-disease interaction.

7.4.2.5 Explorations for drug-drug interactions

There was no evidence of drug-drug interaction.

7.4.3 Causality Determination

Although determining an association of certain safety events with a drug is straightforward, establishing causality is not. Causality generally requires not only an association, but strength of association, temporal match, and biological plausibility. A test often employed is withdrawing the drug and observing whether the associated event abates; rechallenging the subject with the drug should then reinitiate the event in a causal relationship.

The mission of the Agency is to allow only safe and effective drugs to market. Given that causality is difficult to prove, if the Agency has reason to believe that a particular AE is likely to be caused by a drug, the Agency has an obligation to limit the potential harm of this drug.

Fortunately, in the case of OraDiscA, none of the reported AEs were serious and none occurred with a high incidence. In terms of whether the associated AEs such as local irritation, nausea, sore throat, or dizziness are causally related, the best answer is possibly or likely. The most numerous AE, local irritation, is nearly equal between OraDiscA and its vehicle. Because of this, the most likely scenario is that the physical presence of the disk may be causing these local irritations. However because the no-treatment group did was not asked about local irritation from the disk (since there was no disk), there is no comparison to the background local irritation caused by the ulcer itself. A better way to have evaluated the response would have been also asking the no-treatment group about irritation at the aphthous ulcer site in a way that was similar to asking the OraDiscA and vehicle groups.

In terms of the other events such as nausea, sore throat and headache, there were some responses in the no-treatment group, but the lack of blinding certainly biases the response towards a lack of reports. For these events, it is probably most conservative to consider them all possibly or likely related to the study drug.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The 2-mg patch of amlexanox is the only dose of OraDiscA proposed, and the dosing regimen is one patch placed on the area affected by the aphthous ulcer four times per day. Although most individuals only experience one aphthous ulcer at a time, for those who experience multiple concurrent aphthous ulcers, the drug is proposed to be used to treat up to three ulcers at one time, with one OraDiscA placed on each ulcer.

The dose chosen for OraDiscA was identical to the dose for Aphthasol. The 2 mg of amlexanox in each OraDiscA corresponds to the approximate amount of amlexanox in one dab of 5% amlexanox paste, which is currently marketed in the United States. The proposed frequency of four times per day is also identical to the frequency that was proved efficacious for the amlexanox paste; the sponsor suggests that this is the highest frequency of administration with which patients are likely to comply. It would have been ideal to experiment with lower doses since it was expected that this OraDiscA new delivery system would be more efficient than the paste at supplying the same amount of amlexanox to the site and retaining it there longer. Nonetheless, amlexanox was shown in Aphthasol to have a very safe profile, and the Agency had no comments during the IND phase of development about exploring other dosing.

8.2 Drug-Drug Interactions

No drug-drug interactions were uncovered during the review process; based upon testing results, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by cytochrome P450. There are no recommendations for dosing adjustments.

8.3 Special Populations

No formal studies in humans of the effects of drugs on reproduction or pregnancy were performed; similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified. The drug is recommended for pregnancy category B through review of reproduction studies which 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). Those studies 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.

Patients with hepatic and renal insufficiency are not restricted in their use of OraDiscA.

In the pivotal trial, patients who were diabetic or tobacco users were excluded from the trial. The sponsor eliminated diabetics because they did not want the confounding of potential wound healing difficulties; however, it is not clear why smokers were eliminated. Literature suggests a lower incidence in tobacco users than in non-smokers, so it is possible that the sponsor wanted an enriched population by eliminating them. However, with such a high prevalence of smokers in the United States, the studies have eliminated the study of OraDiscA in a large segment of the target population. The sponsor's proposed labeling will be modified to reflect the uncertainty about the effect of OraDiscA on smokers. The exclusion of diabetics should be mentioned in the clinical trials description of the label.

8.4 Pediatrics

The Agency granted a partial waiver of pediatric testing to children under the age of 12. Although children younger than 12 do get aphthous ulcers, the Agency concluded that given that the disk size may pose a safety concern in young children and the need to comply with four times per day dosing, OraDiscA would not be appropriate for individuals under the age of 12.

Patients between the ages of 12 and 17 participated in the OraDiscA studies with a total enrollment of 79 subjects in groups using OraDiscA, 60 subjects assigned to the vehicle disc, and 16 who were in the no-treatment group. Of the 79 subjects on OraDiscA, 25 were in the open label study and experienced 28 consecutive days of exposure; the remaining 51 were in seven-day trials.

The safety data from the clinical trials provides sufficient evidence of OraDiscA's safety in the pediatric population down to the age of 12. The incidence of adverse events affecting the application site was similar for the amlexanox patch and vehicle patch treatment groups. For the pediatric subjects receiving OraDiscA, 3% of these subjects on

OraDiscA reported pain at the application site, compared to 2% in the vehicle group; 3% reported paresthesia in both the OraDiscA and vehicle groups; and 3% of subjects reported headache in the OraDiscA and vehicle group. None of these subjects withdrew due to an adverse event, and none of the events were significant.

Efficacy of OraDiscA was examined in children between the ages of 12 and 17. Although the safety data were adequate to conclude that it is safe for use in children of this age, the sample size was too small in this age group to be conclusive about the efficacy data in children. There is no biological hypothesis or supporting evidence that children would respond differently to amlexanox than adults. However, pediatric trials are always challenging, particularly in cases where compliance is an issue such as this one where the children would need to be placing new disks four times a day for 7 days.

Based upon the strong safety profile of OraDiscA and the lack of literature to suggest that aphthous ulcers in adolescents behave differently than in adults, there is no reason to request further testing in adolescents. In the pediatric section of the label, the information gathered from the clinical trials should be accurately presented, including an adequate demonstration of safety, and the inability to specifically report efficacy in pediatric patients.

8.5 Advisory Committee Meeting

There were no advisory committee meetings in which OraDiscA or any other drug product containing amlexanox was discussed.

8.6 Literature Review

Literature related to the application has been referenced throughout the review as needed. As was discussed in Section 7.2.2.3, most of the literature submitted to this NDA consists of published toxicology studies and papers discussing the etiology and epidemiology of recurrent aphthous ulcers. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is not a need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials that are not included in other sections of the review. The results of a review of the product name from the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) is discussed in Section 9.4 of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

OraDiscA patch (2 mg amlexanox in a patch) has shown adequate evidence of effectively improving the healing of aphthous ulcers. In one placebo-controlled, randomized and blinded clinical trial of seven days duration, a significantly higher percentage of aphthous ulcer patients experienced complete healing on Day 5 of OraDiscA treatment compared to those who were supplied with a vehicle disk. Data from a non-pivotal phase 3 trial were also used to reinforce the pivotal trial efficacy results. OraDiscA has been shown to be safe for its intended use as recommended in the labeling by all tests reasonably applicable to the assessment of safety. These include comparison of adverse events in the clinical trials between groups, reviewing laboratory data, reviewing postmarketing reports from already marketed amlexanox products, and gathering chronic use data from an open label safety trial. Demographic data allowed evaluation of safety and efficacy in subgroups based upon race and gender. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose.

The efficacy results in the 12 – 17 year old pediatric population are inconclusive due to a sample size that is too small for adequate analysis. However, safety was adequately demonstrated, and there is no biological explanation for any difference between the effect in adults and in adolescents.

9.2 Recommendation on Regulatory Action

This new drug application is recommended for approval. The efficacy has been demonstrated through one well-controlled pivotal study. Data gathered was adequate to assess safety, and included not only adverse event monitoring during the trials, but also pre-marketing and postmarketing evaluations for Aphthasol and postmarketing data that was available for oral amlexanox. No Phase 4 commitments will be requested. The sponsor's proposed labeling as submitted in the NDA requires revision before approval.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommended postmarketing risk management activities.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

A review from the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) was completed and sent to the OraDiscA reviewers in the review Division on August 13, 2004. DMETS does not recommend the use of the proprietary name OraDisc™ A due to the possibility of look-alike and sound-alike confusion with Orudis KT, Oralone, Orabase HCA, and Oraqix. On August 16, 2004, the sponsor received these comments via facsimile transmission. There has been no proposal for developing a Medication Guide or Patient Package Insert for OraDiscA.

The appendix to this review includes a line-by-line review of the proposed label, with appropriate markings for every suggested addition and deletion to that text. In the remainder of this section, a summary of the major changes needed in the sponsor's proposed labeling is presented. Refer to the appendix for a line-by-line review.

The major changes to the sponsor's proposed label that the Agency recommends include the removal of the description and results of the non-pivotal trial, the addition of tables in the clinical studies and adverse events section of the label. The storage conditions also need revision per the CMC reviewer.

In the Clinical Studies section, the sponsor had proposed language to describe the results of both the pivotal phase 3 study and a non-pivotal phase 2/3 study. As has been discussed in this review, the non-pivotal study was only used to clarify certain results from the pivotal trial, but due to the formulation difference, not be cited as pivotal. Therefore, the description and results from that nonpivotal trial are eliminated from the label. For the description of the pivotal trial, the sponsor only discussed the results for healing and pain relief at Day 5, which does not provide a balanced assessment of what patients could expect during the entire seven days. Substitution of two tables - one for the healing and one for pain relief that provide a complete and easy-to-read synopsis is preferable. Similarly, the sponsor provides a brief narrative of the adverse reactions observed in the trial. However, a table that shows the distribution of the events in all three arms provides much more information and has been added to the narrative. Because the CMC review determined that 12-month stability was not demonstrated at [ ] the labeling should be changed to reflect the acceptable alternative, 25° C.

9.5 Comments to Applicant

After completing internal team discussion of the sponsor's proposed label, the Agency sent comments from DMETS as well as the review division. These have been incorporated into the label that follows.

10 APPENDICES

10.1 Review of Individual Study Reports

Highlights of the individual studies were discussed in the body of this review. No further review of individual study reports is warranted.

10.2 Line-by-Line Labeling Review

In this section, three sets of the label will be provided. The first label is the sponsor's proposed label (Section 10.2.1). The second label is the Division-revised label (Section 10.2.2).

7 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Fred Hyman
9/24/04 12:52:03 PM
MEDICAL OFFICER

John Kelsey
9/24/04 03:50:00 PM
MEDICAL OFFICER
See Multi-disciplinary Summary which clarifies the extent to which approval is based upon data from studies using the early formulation of the product.

Jonathan Wilkin
9/24/04 04:27:17 PM
MEDICAL OFFICER
See TL Multidisciplinary summary