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APPLICATION NUMBER

NDA 21-727

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-727/N000

Brand Name: OraDisc™
Generic Name: Amlexanox 2 mg, Mucoadhesive Patch
Dosage Form: Mucoadhesive Patch
Dosage Strength: 2 mg
Indication: Treatment of Aphthous Ulcers
NDA Type: Original NDA
Submission Date(s): 12/04/03, 03/04/04, 08/13/2004
Sponsor: Access Pharmaceuticals, Inc.
Reviewer: Chandra S. Chaurasia, Ph.D.
Acting Team Leader: Arzu Selen, Ph.D.
OCPB Division: DPE III (HFD-880)
OND Division: ODE V (HFD-540)

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1. EXECUTIVE SUMMARY

Amlexanox is a benzopyrano-bipyridine carboxylic acid derivative with antiinflammatory and antiallergic properties. It is approved in the United States as an oral paste in 5% strength (Aphthasol) for topical use in aphthous ulcers in adult population with normal immune systems (NDA 20-511, 12/17/96, Glaxo Smith Kline). The drug is available in Japan as an oral tablet (25 mg and 50 mg strengths) for the treatment of asthma and allergic rhinitis, approved in 1987, and as a 0.25% nasal douche and ophthalmic solution for the treatment of local allergic symptoms.

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OraDisc (Amlexanox 2mg, Mucoadhesive Patch) is a topical solid patch formulation that is to be applied to the oral mucosa. Following administration, the patch slowly erodes on the mucosa, releasing the active agent to the area of the aphthous ulcer. Amlexanox from the eroded patch is expected to be swallowed by the subject over the course of 1 to 2 hours. The swallowed amlexanox is absorbed from the gastrointestinal tract to produce systemic serum levels of amlexanox.

To support the clinical safety and efficacy of OraDisc, the Sponsor has conducted pivotal Phase 1 single dose (Study AP-C-1U107) and Phase 3 (Study AP-C-1U-106) multiple dose studies. In addition, clinical safety data of amlexanox from the oral paste and tablet formulations are available.

The basic pharmacokinetic characteristics 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. M-1 metabolite concentrations in serum were approximately 10% of the levels of amlexanox. There was no evidence of any accumulation of amlexanox or M-1 with multiple dosing.

Following topical administration of OraDisc patch, amlexanox exhibits systemic absorption. After normalization for dose, the AUC₀₋₂₄ values for OraDisc were similar to those for amlexanox tablets and for Aphthasol paste, indicating similar systemic exposure. The dose-normalized C_{max} values tended to be lower for the patch than for the Aphthasol paste. The terminal half-life values were very similar for each formulation.

It is noted that the paste is approved for adult population only. In the pivotal Phase 3 trial, efficacy and safety was determined also in adolescents (n=37/303 or 12%). In the pharmacokinetic subset of study AP-C-1U106, 31 subjects were treated with OraDisc. Of these, only 3 were in the age range of 12-18 years. Thus, the number of subjects in the adolescent population is too small to allow a statistical comparison of adult and adolescent exposure values. However, as there were no efficacy or safety differences, pharmacokinetic data from the adolescents which were similar to those from the adult population group, are considered adequate, pharmacokinetic differences would be highly unlikely between the adolescents and the adults for the amlexanox oral patch formulation.

Furthermore, the Sponsor has provided dissolution release profile of OraDisc using USP apparatus 2, at 37°C in 900 mL of the artificial saliva medium. The proposed specification is NLT 75% within 60 minutes. The reported % release of the OraDisc 2 mg patches are [] (range [] and []), at [] and 60 minutes, respectively. The Agency requests the Sponsor to set an interim dissolution specification of NLT(Q) [] at 60 minutes.

1.1 Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of the amlexanox mucoadhesive patch, 2 mg and found it to be acceptable for meeting the requirements of 21CFR320. The Sponsor is requested to set an interim dissolution specification of NLT(Q) [] of the labeled content of the drug to be dissolved in 60 minutes.

1.2 Phase IV Commitment: None requested at this time.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The Sponsor, Access Pharmaceuticals, is seeking approval of OraDisc (amlexanox mucoadhesive patch 2mg) for treatment of aphthous ulcers in adults and adolescents 12 years of age and older. The NDA 21-727 is a 505 (b)(2) application. The approved product Amlexanox Oral Paste 5% (NDA 21-511) has identical dosing regimen and indication for adult population only. It is noted that the 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

In support of this application the sponsor has submitted the following clinical studies:

- Protocol AP-C-1U107:** A phase 1 study to investigate the single dose pharmacokinetic characteristics of OraDisc 2 mg.
- Protocol AP-C-1U106:** A phase 3 study to determine the safety and efficacy, and to measure serum levels of amlexanox after multiple application of OraDisc 2 mg patches.

The phase 1 study AP-C-1U107 was conducted to investigate the pharmacokinetics and safety of amlexanox OraDisc, 2 mg in adult population (≥ 18 years of age, N=18) with minor aphthous ulcers after a single application to 1-3 aphthous ulcers. Mean serum PK parameters are presented in Table 1 below.

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

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

The highest observed serum concentration of amlexanox for a subject who received one patch was [] ng/mL, and the lowest measurable C_{max} was [] ng/mL. The mean concentration was 45.4 \pm 39.6 (range [] mL, N=14). The mean values for AUC₀₋₂₄ for one and three OraDiscs were 258 \pm 238 and 605 \pm 356 ng·hr/mL, respectively.

The C_{max} value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As

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indicated in the results, there is a substantial inter-subject variability in the C_{max} values presumably due to individual variation in the amount and rate of systemic absorption.

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 OraDisc, and a slow systemic absorption of amlexanox from the drug product.

Considering the AUC data from the one and three OraDisc treatment, there is no trend of nonlinearity over the range of 2 to 6 mg dose, however, the number of subjects (N=3) in the 6 mg dose (i.e., 3 OraDiscs) is too small to reach any conclusion on the dose proportionality.

The secondary objective of this study was to collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers. Following application, the patch slowly erodes in the mouth, generally disappearing entirely in 50-80 minutes. During this process, the patient may feel some type of debris due to patch erosion.

The phase 3 study AP-C-1U106 was evaluator-blinded, randomized, parallel-group study with the following objectives:

- To determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers.
- To evaluate the safety of amlexanox OraDisc by determining the frequency of treatment-emergent adverse events.
- To measure serum levels of amlexanox after multiple applications of OraDisc.

The study included male or females of at least 12 years of age with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve. Patients were randomized to 3:3:1 to active patches, vehicle patches or no-treatment. The "no-treatment" arm was included in order to demonstrate that the vehicle patch did not have a worsening, irritating effect on the aphthous ulcers.

Patches were applied four times a day (after each meal and at bed time) directly over the designated ulcer(s) for 7 days or until all treated ulcers healed, whichever occurred first. Up to a maximum of 3 ulcers were treated per patient. Blood samples were collected on Day 4 prior to the first patch application, and two hours after the first patch application. A total of 152 samples were collected from 77 patients at 7 study centers. Of these samples, 60 were obtained from 31 patients in the Amlexanox OraDisc group. All but 2 provided both pre-dose and 2-hour post-dose samples. Sixty-six samples were obtained from 33 patients and 26 samples were obtained from 13 patients from the vehicle patch and no treatment groups, respectively. Of the 31 patients treated with OraDisc only 3 were in the age range of 12 to 18 years. No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of — ng/mL. The PK results obtained from the OraDisc-treated group is summarized in the Table 2. below:

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Table 2. 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 ()	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 ()

As noted in the Table above, prior to first dose on Day 4, the maximum pre-dose concentrations (C_{min}) were () ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 were () ng/mL. The inter-subject variability was high in all groups. Furthermore, because of low number of subjects in the 2 and 3 patch-treatment groups, comparison for dose-proportionality is not possible.

The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL. This is lower than the reported C_{max} value for the approved amlexanox product 5% paste (116 ±71.2 ng/mL).

As mentioned above, 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 amlexanox concentrations in this group are comparable to the values seen in the adults.

In addition to the above pivotal studies, the firm has provided results of pharmacokinetic data from the following clinical trials:

- Study No. AP-C-9E03; A phase 2/3 investigator-blind, randomized, parallel-group study to determine the effects and serum levels of amlexanox disc 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle discs or no treatment in patients 12 years of age or older.
- Study No. 34,787-110: A phase 1 study to determine the pharmacokinetics of amlexanox after a single topical administration of 100 mg of 5% amlexanox paste to minor aphthous ulcers.
- Study No. BD98-006: A phase 1 study in children 8 to 12 years of age to determine the pharmacokinetics of amlexanox after a single topical administration of 5% amlexanox paste to the oral mucous membrane.

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In Study AP-C-9E03 an Early Formulation patch was applied qid for 7 days. Serum levels of amlexanox was determined after 3 full days of treatment before the first application and 1 hour post-dosing on Day 4. As agreed upon between the Sponsor and Agency, the above study AP-C-9E03 is not being considered for approval of this NDA. The PK results from this study have been summarized in the QBR section 2.1 for supportive purpose only.

Study No. 34,787-110 and BD. 98-006 were reviewed by the Agency as part of the NDA 20-511 and IND [], respectively. The PK results of these studies are summarized in the Table 4 below. PK results from the amlexanox oral tablet are also provided for reference purpose.

Single-Dose Pharmacokinetics of amlexanox from 5% oral paste and tablet formulations

Study No	Formulation/Dosage Form	Dose Used in Study	AUC ₀₋₂₄ (ng·hr/mL/mg)	C _{max} (ng/mL/mg) [ng/mL]	T _{1/2}
34,787-110 Adults Healthy Subjects (19-50 yrs)	Aphthasol Paste 5%	5 mg	629 ± 366 (N=12)	117 ± 71 (N=12)	4.1
Phase 1 , Healthy Pediatrics (8-12 yrs)	Aphthasol Paste 5%	5 mg	1026 ± 550(AUC ₀₋₈) 205*	469 ± 202 93*	1.2
AA-673/X-108/Adults, healthy subjects (31-48 yrs)	Tablets/Oral	12.5 mg 25 mg 50 mg 100 mg	95* 163* 268* 148*	39.2* 45.6* 95.6* 28.4*	-

*Normalized to 1 mg Amlexanox

Dissolution:

The applicant has conducted dissolution testing using the USP apparatus in artificial saliva medium. The Sponsor's proposed specification is NLT [] of the active ingredient released within 60 minutes.

Since product is designed to erode in the mouth after approximately one hours, and the average time for almost complete erosion of OraDisc patch is [] minutes, the firm's proposed specification of NLT [] active release within 60 min appears reasonable.

Chandra S. Chaurasia, Ph.D. _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

Date: _____

RD/FT Initialed by Arzu Selen, Ph.D.. _____
Deputy Director, DPE-III/
Acting Team Leader HFD880

Date: _____

CC: NDA 21-727, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (J. Lazor, A. Selen)

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2. Question Based Review

2.1 General Attributes of Amlexanox

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

This application is based on the following features that would support an NDA filing under the section 505(b) (2) of the Federal Food Drug and Cosmetic Act.

Amlexanox Oral Paste 5% is approved in the United States for topical use in aphthous ulcers in **adult population** with normal immune systems (NDA 20-511, 12/17/96, Glaxo Smith Kline). The drug is available in Japan as an oral tablet for the treatment of asthma, and as a nasal douche and ophthalmic solution for the treatment of local allergic symptoms.

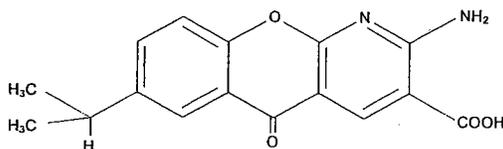
The primary focus of this NDA is to establish efficacy and safety of the oral mucoadhesive patch formulation in adolescent and adult populations. The 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

To establish systemic exposure the Sponsor has provided PK results of a single dose Phase 1 and a multiple dose Phase 3 studies.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

OraDiscTM 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, sodium carboxymethylcellulose
Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2, 3-b] pyridine-3-carboxylic acid.

Structural formula



Empirical Formula: C₁₆H₁₄N₂O₄

Molecular Weight: 298.30

Physicochemical Properties: Amlexanox is an odorless, white to yellowish-white crystalline powder insoluble in water.

2.1.3. What are the proposed mechanism of action and therapeutic indication of amlexanox?

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Mechanism of Action: The mechanism of action by which amlexanox accelerates healing of aphthous ulcers is unknown. *In vitro* studies have demonstrated amlexanox to be a potent inhibitor of the formation and/or release of inflammatory mediators (histamine and leukotrienes) from mast cells, neutrophils, and mononuclear cells.

Indication: Amlexanox OraDisc™ is indicated for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older.

2.1.4 What is the proposed dosage and route of administration?

Dosage and Administration: The proposed dose for OraDisc™ is one patch four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and before bedtime. In case of multiple ulcers, application of one OraDisc™ patch to each ulcer is indicated. Multiple patches may be used at one time. Use of the medication should be continued until the ulcer heals.

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Sponsor conducted two pivotal studies to support the clinical pharmacology aspects of the OraDisc patch.

The phase I study (no. AP-C-1U107) was conducted to investigate the pharmacokinetic and safety characteristics of Amlexanox OraDisc 2 mg in 18 subjects with minor aphthous ulcers after a single application to 1-3 aphthous ulcers. In addition, the study also collected information on the retention and resorption properties of OraDisc when applied to the aphthous ulcers.

The phase III study (No. AP-C-1U106) was a multi-center, multi-dose, evaluator-blinded, parallel-group, vehicle-controlled, no-treatment-controlled, parallel-group study in male or females at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve. The study was conducted to determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers. A subset of the study population was used to measure serum levels of amlexanox after multiple applications of OraDisc.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

As this NDA is a line extension of the approved amlexanox 5% paste, with the same indications and dosing regimen, same endpoints were studied.

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2.2.3 Are the active moiety in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the Sponsor measured the amlexanox in clinical pharmacology studies. See Analytical section for more details.

2.2.4. Exposure-response evaluations

Since amlexanox was already approved as a paste, information included in this NDA is specific to characterization of the product in adolescent and adult patients.

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Based on NDA 20-511 for amlexanox paste, no new exposure-response information has been submitted for the current mucoadhesive patch dosage form. The pharmacokinetics of OraDisc are consistent with the pharmacokinetics of Aphthasol. The exposure-response relationships for efficacy are expected to be comparable to those seen with Aphthasol.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

A direct assessment of the exposure-response relationship for safety was not contained in this NDA.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Amlexanox is not known to affect the QT interval.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As this is a line extension with no changes in either dosing or indications, this does not apply here.

2.2.5 What are the pharmacokinetic characteristics of the drug and its metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single Dose PK Study No. AP-C-1U107

Mean serum for PK parameters are presented in Table 1 above under Summary of Important Clinical Pharmacology and Biopharmaceutics Findings in Section 1 of this review. The highest observed serum concentration of amlexanox for a subject who received one patch was 138 ng/mL, and the lowest measurable C_{max} was 10 ng/mL. The mean concentration was 46.4 ± 39.6 (range 10 - 138) ng/mL, N=14).

Of the 14 subjects who received one OraDisc, one subject (#13) did not have measurable concentration of amlexanox at any sampling time, and 4 subjects (#8, 14, 17 and 18) had concentrations of 10 ng/mL or less at all sampling times. The mean C_{max} and AUC₀₋₂₄ of amlexanox in 13 subjects with measurable levels, were 45.4 ng/mL (range 10 - 138) and 258 ng.hr/mL (range 10 - 258), respectively.

The C_{max} value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As

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indicated in the results Table, there is a substantial inter-subject variability in the C_{max} values presumably due to individual variation in the amount and rate of systemic absorption. However, the mean C_{max} values tended to increase with increasing number of OraDisc applied with a statistically significant difference ($p = 0.027$, two sample t-test) when comparing the C_{max} values for one and three OraDiscs.

The mean half-life values were 4.5 ± 2.0 and 8.8 ± 3.5 for subjects who received one or three patches, respectively, the half-life for the one subject who received two patches was 3.2 hr.

Multiple Dose PK Study No. AP-C-1U106

Pharmacokinetic results: No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of \sim ng/mL. The PK results obtained from the OraDisc-treated group is summarized in Table 2 above under Summary of Important Clinical Pharmacology and Biopharmaceutics Findings in Section 1.

Prior to first dose on Day 4, the maximum pre-dose concentrations (C_{min}) were \leq and \leq ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 concentrations were \leq ng/mL. The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL.

Due to smaller sampling size, with two patch (N=5) and three (N=2) patch treatments, no conclusive observation on a dose-proportionality of systemic availability could be inferred. The inter-subject variability was high in all groups.

2.2.5.2 How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable.

2.2.5.3 What are the characteristics of drug absorption?

T_{max} occurred at approximately 3 hr (mean T_{max} of 2.8 ± 1.7 , 3.0 and 3.0 ± 1.0 hr for one, two and three OraDisc, respectively). Most subjects observed a lag time (T_{lag}) of 0-0.5 hours. A T_{lag} of 0-1 hour was observed in 9/13 (69%) of the subjects receiving one OraDisc treatment. Based on the reported T_{lag} (0-1 hr) and mean T_{max} (\sim 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 OraDisc, and a slow systemic absorption of amlexanox from the drug product.

2.2.5.4 What are the characteristics of drug distribution?

Drug distribution characteristics are included in NDA 20-511 for amlexanox oral paste, no new information has been submitted for the current mucoadhesive dosage form. The drug distribution characteristics of the patch formulation are expected to be comparable to those in oral paste.

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2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted for this application.

The basic pharmacokinetic characteristics of amlexanox were determined in the studies with amlexanox tablets marketed in Japan since 1987. Results of PK studies with amlexanox tablets were considered during the review and approval of the 5% amlexanox paste (NDA20-511, Report No. AA-673/X-108). Serum and urine levels of amlexanox, its M-1 metabolite and conjugates were measured following 12.5, 25, 50 and 100 mg tablets. The urinary excretion of M-1 metabolite was similar for all doses, ranging from 5.3 to 9.7%. Studies done with amlexanox paste 5% showed that a single dose of 100 mg of paste (a dose considered approximately equivalent to 2 mg patch), a total of 17%± 12% was recovered in the urine. Amlexanox and its conjugates accounted for 7.8% of the dose, the metabolite M-1 accounted for 6.25% of the dose, and an additional 3% of the dose was conjugates of M-1.

2.2.5.6 What are the characteristics of drug metabolism?

The basic pharmacokinetic characteristics of amlexanox were determined in the studies with amlexanox tablets marketed in Japan since 1987. Systemically absorbed amlexanox is metabolized by hydroxylation to form the M-1 metabolite and some unidentified conjugates. M-1 metabolite concentrations in serum were approximately 10% of the serum amlexanox concentrations.

2.2.5.7 What are the characteristics of drug excretion?

Based on NDA 20-511 for amlexanox oral paste, no new information has been submitted for the current mucoadhesive dosage form.

Please also see the above Section 2.2.5.5

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity in the dose-concentration relationship?

Due to smaller sampling size, with two patch (N=1, Study No. AP-C-1U107, and N=5 Study No. AP-C-1U106) and three patch (N=3, Study No. AP-C-1U107 and N=2, Study No. AP-C-1U106) treatments with OraDisc, no conclusive results on the systemic availability can be inferred.

However, the mean C_{max} values tended to increase with increasing number of OraDisc applied with a statistically significant difference (p = 0.027, two sample t-test) when comparing the C_{max} values for one and three OraDiscs in the Phase I Study No. AP-C-1U107.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

Not applicable.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

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As indicated in the PK results, there is a substantial inter-subject variability in the C_{max} and AUC₀₋₂₄ values presumably due to individual variation in the amount and rate of systemic absorption.

2.3. Intrinsic Factors

Other than inclusion of adolescent subjects in the Phase 3 trial AP-C-U106 no additional information that will allow assessment of intrinsic factors has been submitted.

2.4. Extrinsic factors

On August 13, 2004, the Sponsor submitted a 4-month safety update report (project no. 104341) on the potential of amlexanox to inhibit the activity of various CYP450 isozymes. Based on the results of this report, the effects of 10 uM amlexanox on CYP450 1A2, 2C19, 2D6 and 3A4 were less than 10% inhibition or stimulation. In the pivotal clinical trial, the maximum concentration of amlexanox was less than 400 ng/ml or 1.3 uM. There were no appreciable effects of amlexanox at 0.1 or 1 uM concentration on CYP 450 2C9 isozyme. Thus, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by CYP450 1A2, 2C9, 2C19, 2D6 and 3A4.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

The applicant has not provided any permeability data. As noted above under physical properties, amlexanox is insoluble in water.

2.5.2. What is composition of the to-be-marketed formulation?

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

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The proposed formulation for the to-be-marketed oral patch is same as the formulation used in the pivotal clinical studies.

2.5.4 What moieties should be assessed in bioequivalence studies?

No BE studies were done. For the PK measures in bioavailability studies, the active moiety amlexanox was assessed.

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2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable to the drug product as OraDisc is to be used topically.

2.5.7 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Yes., the applicant has conducted dissolution testing using the following method.

Apparatus: USP Apparatus 2,

Rotation: 75 rpm

Medium: Artificial Saliva* Volume 900 mL

Specification: NLT 75% of the active ingredient released within 60 minutes.

*Composition of the artificial saliva: 75

]

The dissolution results are provided in the Table below:

In Vitro Dissolution with New Formulations

Study No.	Batch No.	No. of Units	Mean %±SD Dissolved (Range)			
			15 min	30 min	45 min	60 min
AP 03-10-01	BMS 4259	N=6	75			75
			75			75

The dissolution study was conducted using the patches from Batch BMS-4259 that was also used in phase 3 clinical trial study.

The product was designed to erode in the mouth after approximately one hour. The data from Study AP-C-1U107 show that it took an average of 75 minutes for half the OraDisc patch to erode. By an average of 75 minutes most of the patch had eroded. Based on the dissolution results, the firm justifies that the proposed specification of NLT 75% active release within 60 min is a reasonable measure of the ability of the patch to deliver the majority of the active components within the residence time of the patch in the mouth.

As reported by the Sponsor (Section 3.2.P.2.8), the % release of the OraDisc 2 mg patch (N=6) are 75 (range 75-75) and 75, 75, at 15 and 60 minutes, respectively. The Agency requests the Sponsor to set an interim dissolution specification of NLT(Q) 75, at 60 minutes.

2.6 Analytical Section

2.6.1 Were relevant metabolite concentration measured in the clinical pharmacology and biopharmaceutics studies?

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The applicant measured the active moiety amlexanox in serum samples in all pharmacokinetic studies included in this submission. Urinary data were submitted in the data from oral paste and tablet formulation submissions and no urinary metabolites in the studies in this submission were measured.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis of that decision, and is it appropriate?

- Total amlexanox concentrations in serum were measured.

2.6.3 Were the analytical procedures used to determine drug concentration in this NDA acceptable?

Yes. Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection. The limit of detection (LOQ) was [] ng/mL. Calibration standards employed drug concentrations from [] ng/mL with a correlation coefficient of 0.9996. Intra- and inter-run accuracy ranged [] respectively. The intra- and inter-run precision were [] respectively. The long term frozen stability in human serum at -20° C for up to 12 months and freeze thaw stability for [] were acceptable. The applicant has provided adequate documentation of method validation and in-study validation.

3. Detailed Labeling Recommendations

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7 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Review

1. Phase 1 Study with the Final Formulation Single Dose.

Protocol AP-C-1U107: A phase I study to investigate the pharmacokinetic characteristics of Amlexanox OraDisc 2 mg, in 18 subjects with minor Aphthous ulcers after a single application to 1-3 aphthous ulcers.

Study Design: This was a Phase I, single-center, open-label, single-group, in male and female at least 18 years of age in general good health and presenting with at least one minor aphthous ulcer.

Objectives: Primary: To investigate the pharmacokinetics and safety of amlexanox OraDisc, 2 mg, following a single oral application of 1 to 3 mucoadhesive patches in subjects with minor aphthous ulcers.

Secondary: To collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers.

Study Center: U

Investigator:

Analytical Center: J

Study Subjects: Eighteen subjects (10 females and 8 males) at least 18 years of age in general good health and presenting with at least one minor aphthous ulcer were included in the study. All 18 subjects completed the study. The number of ulcers at baseline varied from 1 to 4 with most subject (14) having only one ulcer. Baseline oral status, number of ulcers and size of ulcers at study entry are described in detail in Module 1.5, Vol. 1.2, Sec. 5.3.2.2, pp. 32.

The mean and range for age, weight and height were 36 years (range 18-63), 76 kg (range 54-98) and 174 cm (range 160-191), respectively. There were 11 Caucasian (5 males and 6 females) and 7 Black (2 males and 5 females). Inclusion and exclusion criteria are described Module 5, Vol. 1.2, Sec5.3.3.2, pp. 16-17.

Dosage and Administration: Each subject applied one mucoadhesive patch to each ulcer up to a maximum of 3 patches. Disposition of subjects entered into study was as follow:

	Male	Female	1 Patch	2 Patches	3 Patches
No. of subjects enrolled	8	10	14	1	3
No. of subjects completed the study	8	10	14	1	3

Study Dates: Clinical study was performed between July 2, 2002 to January 11, 2003

Analytical: Samples were analyzed between Feb 26, 2003 to March 05, 2003.

Drug Formulations: Test: Amlexanox OraDisc: Lot No. BMS 4257/CSI 10594.

Criteria for Evaluation:

Pharmacokinetics: Serum samples 7.0 mL pre-dose (0) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose after application of the adhesive mucosa.

Retention, Resorption: On Day 1 at 0. 5. 15, 30, 45, 60, 75, 90 and 120 minutes after application of the mucoadhesive patch, an evaluator recorded the levels of:

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- retention on a 6-point scale of 0-5, and
- resorption (solid particle free in the oral cavity at any time: yes/no).

Analytical Determinations:

Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection. The limit of detection (LOQ) was 1 ng/mL. Calibration standards employed drug concentrations from 1 ng/mL with a correlation coefficient of 0.9996. Intra- and inter-run accuracy ranged 1 respectively. The intra- and inter-run precision were 1 respectively. The long term frozen stability in human serum at -20 C for up to 6 months and freeze thaw stability for 1 were acceptable. The mean accuracy for the 5- and 20-fold diluted samples were within ±15%. No interference was noted with regards to selectivity and specificity. The analytical validation is described in detail in Module 5, Vol. 1.2, 1.6, and 1.7.

Results:

Patch Retention and Resorption Scores:

Summary statistics for patch retention scores are presented in the following Table and Figure. A score of 3 and 2 meant that the patch has eroded to 75-50% and 50-25% of its original surface area, respectively.

Mean (S.D.) Patch Retention Score* over Time

Time after Patch Application (minutes)	Mean (S.D.) Retention Score		
	All (N=18 subjects, 25 patches)	Female (N=10 subjects, 15 patches)	Male (N=8 subjects, 10 patches)
0	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
5	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
15	4.6 (1.8)	4.6 (0.5)	4.7 (0.5)
30	3.3 (1.8)	3.2 (1.7)	3.5 (1.9)
45	2.6 (1.7)	2.5 (1.5)	2.6 (2.0)
60	1.8 (1.6)	1.9 (1.5)	1.7 (1.9)
75	1.2 (1.1)	1.4 (1.0)	0.9 (1.3)
90	0.8 (1.0)	0.7 (1.0)	0.8 (1.1)
120	0.2 (0.5)	0.2 (0.4)	0.2 (0.6)

*Retention scale:

5 Complete patch

4 Almost complete patch (<100% to 75% of original size)

3 Gelatinous mass (75% to 50% of original size)

2 Gelatinous mass (50% to 25% of original size)

1 Gelatinous residue or debris

0 No observable material/residue

In 3 subjects, the patch was dislodged between 15 to 30 minutes after application. Subjects 13 and 18 reported the patch adherence to the teeth and Subject 17 the patch dislodged while the subject was blowing his nose. The study evaluator could not confirm whether the loose patches were swallowed or expelled after they were dislodged.

Based on the interpolation of the data, it took an average of 47 minutes to erode half of the patch and 82.5 min to erode all of the patch.

Based on results of statistics for patch resorption (presence or absence of loose particles in the oral cavity) a majority of subjects (12/18, 66.7%) reported feeling some type of debris during the 2 hours of observation.

Pharmacokinetic Results:

Mean and individual serum PK parameters are presented in Tables 3 and 4, and serum-amlexanox concentration profile is depicted in Figure 1 below. The values for C_{max} and AUC₀₋₂₄ were normalized for dose and body surface area. The highest observed serum concentration of amlexanox for a subject who received one patch was 138 ng/mL, and the lowest measurable C_{max} was 39.8 ng/mL. The mean concentration was 45.4 ± 39.6 (range 39.8 - 138) ng/mL, N=14).

Of the 14 subjects who received one OraDisc, one subject (#13) did not have measurable concentration of amlexanox at any sampling time, and 4 subjects (#8, 14, 17 and 18) had concentrations of 10 ng/mL or less at all sampling times. The mean C_{max} and AUC₀₋₂₄ of amlexanox in 13 subjects with measurable levels, were 45.4 ng/mL (range 39.8 - 138) and 258 ng.hr/mL (range 138 - 605), respectively.

The C_{max} value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As indicated in the results Table 3 below, there is a substantial inter-subject variability in the C_{max} values presumably due to individual variation in the amount and rate of systemic absorption. However, the mean C_{max} values tended to increase with increasing number of OraDisc applied with a statistically significant difference (p = 0.027, two sample t-test) when comparing the C_{max} values for one and three OraDiscs.

T_{max} occurred at approximately 3 hr (mean T_{max} of 2.8±1.7, 3.0 and 3.0±1.0 hr for one, two and three OraDisc, respectively). Most subjects observed a lag time (T_{lag}) of 0-0.5 hours. A T_{lag} of 0-1 hour was observed in 9/13 (69%) of the subjects receiving one OraDisc treatment. The mean half-life values were 4.5 ± 2.0 and 8.8 ± 3.5 for subjects who received one or three patches, respectively, the half-life for the one subject who received two patches was 3.2 hr. The T_{max} and T_{lag} were very similar in both genders with no statistical difference (p > 0.3 for both parameters). There were no significant differences in the values of K_e and t_{1/2} also (p ≥ 0.5).

The mean values for AUC₀₋₂₄ for one and three OraDiscs were 258 ± 238 and 605 ± 356 ng-hr/mL, respectively.

Table 3. Mean Pharmacokinetic Parameters Phase 1 Study AP-C-1U107

Parameter	One Patch 2 mg	Two Patches 4 mg	Three Patches 6 mg	Male (All doses)	Female (All doses)
C _{max} (ng/mL)	N=14	N=1	N=3	-	-
Mean ±SD	45.4±39.6	138	168.3±191.5	-	-
Median (range)	39.8 [39.8 - 138]		79.9 [39.8 - 138]		
T _{max} (hr)	N=13	N=1	N=3	N=8	N=9
Mean ±SD	2.8±1.7	3	3.0±1.0	2.5±0.9	3.1±1.9

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Median (range)	2 (1-8)		3 (2-4)	2.5 (1-4)	3 (2-8)
T_{lag} (hr)	N=13	N=1	N=3	N=8	N=9
Mean ±SD	1.0±0.6	1	1.0±0.9	1.1±0.6	0.8±0.5
Median (range)	1.0 []		0.5 []	1.0 []	0.5 []
AUC₀₋₂₄ (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	N=4	N=7
Mean ±SD	4.5±2.0	3.2	8.8±3.5	4.7±2.3	6.1±3.4
Median (range)	4.5 []		10.3 []	4.1 []	5.0 []

Table 4 Individual Pharmacokinetic Measures for Single Dose Phase Study No.AP-C-1U107

Table 12-5: Non-compartmental Pharmacokinetic Parameters by Subject

Pat. I.d.	Age, Sex	Weight (kg)	Height (cm)	BSA (m ²)	Dose (mg/m ²)	C _{max} (ng/mL)	Normalized C _{max} (ng/mL·Y (mg/m ²))	T _{max} (hour)	T _{lag} (hour)	AUC ₀₋₂₄ (ng·hr/mL)	Normalized AUC ₀₋₂₄ (ng·hr/mL·Y (mg/m ²))	r ²	k _e (hr ⁻¹)	t _{1/2} (hour)	AUC _(0-∞) (ng·hr/mL)
ONE PATCH															
01	24, F	53.7	170	1.62	1.24										
02	24, M	86.6	186	2.11	0.95										
03	24, F	70.9	178	1.88	1.06										
05	40, M	76.2	174	1.91	1.05										
07	60, F	71.6	169	1.82	1.10										
08	31, M	89.5	191	2.19	0.91										
11	28, M	73.7	185	1.97	1.02										
12	53, F	65.8	172	1.78	1.13										
13	26, F	86.6	168	1.96	1.02										
14	42, M	98.0	181	2.19	0.92										
15	32, F	58.2	160	1.60	1.25										
16	27, F	84.1	171	1.96	1.02										
17	18, M	71.4	178	1.89	1.06										
18	37, M	81.4	171	1.94	1.03										
TWO PATCHES															
09	53, F	74.6	161	1.79	2.24										
THREE PATCHES															
04	24, F	61.4	170	1.71	3.51										
06	48, F	69.9	176	1.85	3.24										
10	63, M	94.5	179	2.13	2.81										

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* Numbers in italics are considered questionable due to very poor fit of data to regression line for half-life ($r^2 < 0.90$)
** NC = not calculated
Source: Data Listing 16.2.8 and Pharmacokinetic Methods Appendix 16.1.6.

Access Pharmaceuticals, Inc.
New Drug Application, Amlexanox Oradisc™, 2 mg
STUDY AP-C-1U107
Single-dose Pharmacokinetic Study of Amlexanox Oradisc™ in Subjects with Aphthous Ulcers
Module 5, Volume 1.2, Section 5.3.3.2.2
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Figure 1 Mean Plasma Amlexanox Concentration-Time Plot: Phase I Study AP-C-107

Access Pharmaceuticals, Inc.

New Drug Application, Amlexanox OraDisc™, 2 mg

STUDY AP-C-1U107

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Module 5 Volume 1.2 Section 5.3.3.2.2

Single-dose Pharmacokinetic Study of Amlexanox OraDisc™ in Subjects with Aphthous Ulcers

Figure 12-3: Linear Plot of Mean Serum Concentrations of Amlexanox by Dose Group

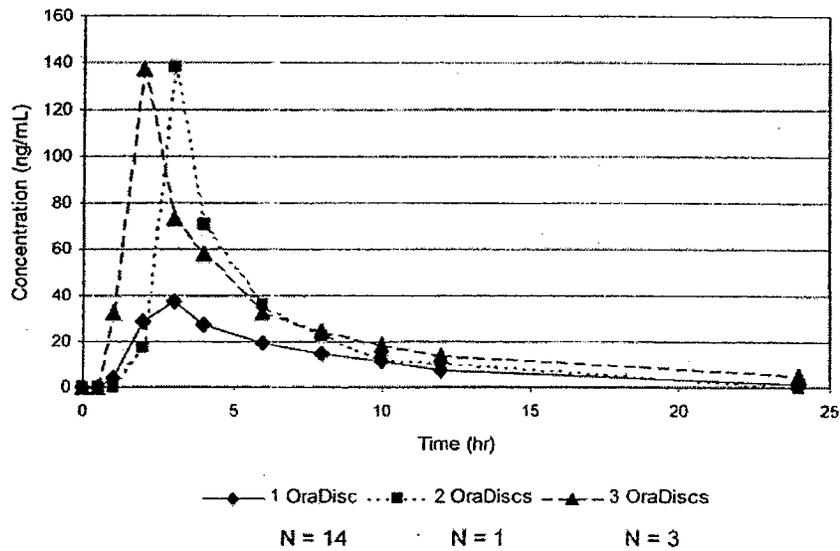
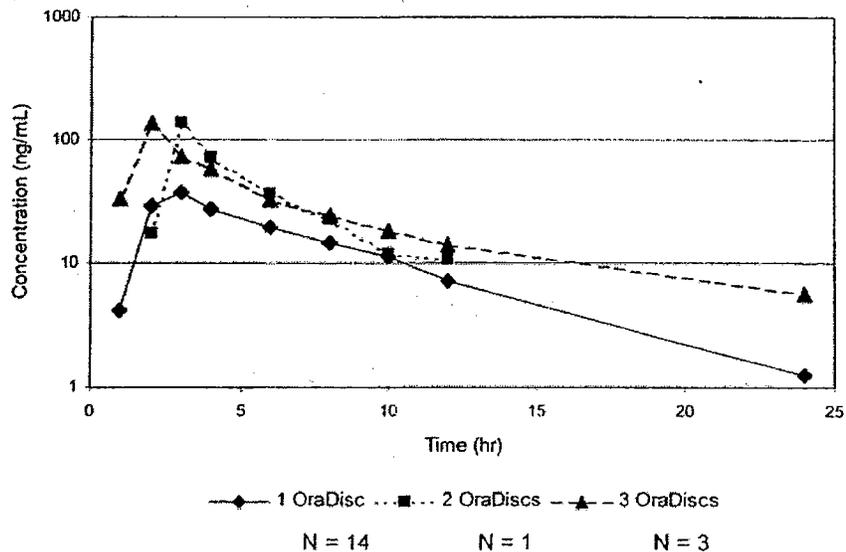


Figure 12-4: Semilog Plot of Mean Serum Concentrations of Amlexanox by Dose Group



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Amlexanox 2 mg Patch, DFS Copy

Comments

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

Considering the AUC data from the one and three OraDisc treatment, there is a no trend of nonlinearity over the range of 2 to 6 mg dose, however, the number of subjects (N=3) in the 6 mg dose (i.e., 3 OraDisc) is too small to reach any conclusion on the dose proportionality.

With regards to effect of gender on the pharmacokinetic of OraDisc, there appears to be more absorption of amlexanox in females than in males. However, there appears to be no gender effect on the rate of elimination of amlexanox from the OraDisc treatment.

2. Phase 3 Study with New Formulation Multiple Dose.

Protocol AP-C-1U106: A phase 3 evaluator-blinded, randomized, parallel-group study to determine the effects the Amlexanox Mucoadhesive patch, OraDisc 2 mg on the healing of recurrent minor aphthous ulcers as compared with vehicle Mucoadhesive patches or no treatment.

Study Design: This was a Phase 3, multi-center, multi-dose, evaluator-blinded, parallel-group, vehicle-controlled, no-treatment-controlled, parallel-group study in male or females at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve, patients were to have at least one identifiable ulcer of the oral mucosa that has developed within 36 hours prior to enrollment. Patients were randomized to 3:3:1 to active patches, vehicle patches or no-treatment. The "no-treatment" arm was included in order to demonstrate that the vehicle patch did not have a worsening, irritating effect on the aphthous ulcers.

Objectives:

- To determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers (9s).
- To evaluate the safety of amlexanox OraDisc by determining the frequency of treatment-emergent adverse events.
- To measure serum levels of amlexanox after multiple applications of OraDisc.

Secondary: To collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers.

Study Center: Twenty-six study centers in the US.

Analytical Center: L

3

Study Subjects: Seven hundred and one patients at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve, patients were to have at least one identifiable ulcer of the oral mucosa that has developed within 36 hours prior to enrollment.

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Amlexanox 2 mg Patch, DFS Copy

Of the 701 patients randomized, 458 were women (65%) and 243 (35%) were men. Ages ranged from 12 to 75 with a mean age of 29.3 years and a median of 26. A majority of patients were Caucasians 601(86%), 54 were Hispanic (8%), 14 (2%) were Asian and 15 (2%) were African American, and 17 (2%) were of mixed race. Details of demographic characteristics are reported in Module 5, Vol 1.3, Sec 5.3.5.1, pp 54.

Disposition of patients entered into study is as follow:

		OraDisc	Vehicle	No Treatment	Overall
No. of patients randomized		303	301	97	701
By Age Group	12-14 yrs	15	27	7	49
	15-17 yrs	22	22	5	49
	18-64 yrs	263	248	84	595
	≥ 65 yrs	3	4	1	8
No. of patients completed the study		284	290	89	663
	12-17 yrs	36	49	12	97
	≥ 18 yrs	248	241	77	566
No. of patients withdrew from the study		19	11	8	38
	12-17 yrs	1	0	0	1
	≥ 18 yrs	18	11	8	37
Reasons for withdrawal					
Worsening of condition		2	0	0	2
Adverse Events		0	4	0	4
Patients request		8	2	7	17
Protocol violation		3	2	0	5
Lost to follow up		4	1	1	6
Other reason		2	2	0	4

Dosage and Administration: Patches were applied four times a day (after each meal and at bed time) directly over the designated ulcer(s) for 7 days or until all treated ulcers healed, whichever occurred first. Up to maximum of 3 ulcers were treated per patient.

Dosage: (1) Amlexanox patch containing 2 mg of amlexanox, (2) Vehicle patch, or (3) No treatment.

Duration of patient participation: 7 days or until all treated ulcers healed, whichever occurred first.

Drug Formulations:	Lot Numbers.:	Amlexanox OraDisc	Vehicle
		BMS-4257	BMS-4254
		BMS-4258	BMS-4255
		BMS-4259	BMS-4256

Inclusion and Exclusion Criteria are provided on page 27-28, Module 5, Vol 1.3.

Rationale for Dose Selection and Dosage Regimen: The 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%, which is currently marketed in the United States. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

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Amlexanox 2 mg Patch, DFS Copy

Study Dates: Clinical study was performed between June 3, 2002 to March 23, 2003

Analytical: Samples were analyzed between April 07, 2003 6 and April 18, 2003.

Analytical Determinations:

Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection by [redacted] as described above for study AP-C-1U107.

Pharmacokinetic Criteria for Evaluation:

Pharmacokinetics: The blood samples were collected on Day 4 at the following time points to estimate the trough and peak levels:

Prior to the first patch application, and two hours after the first patch application. A total of 152 samples were collected from 77 patients at 7 study centers (for details please see pages 36-37, and page 81-82. Module 5, Vol. 1.3). Of these samples, 60 were obtained from 31 patients in the Amlexanox OraDisc group. All but 2 provided both pre-dose and 2-hour post-dose samples. Sixty-six samples were obtained from 33 patients and 26 samples were obtained from 13 patients from the vehicle patch and no treatment groups, respectively. Of the 31 patients treated with OraDisc only 3 were in the age range of 12 to 18 years.

Pharmacokinetic results: Mean and individual serum concentrations from the patch treatment group are presented in Tables 5 and 6 below. No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of [redacted] ng/mL. The PK results obtained from the OraDisc-treated group is summarized in the Table below:

Table 5. Mean Pharmacokinetic Parameters for the Patch Treatment Group 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 [redacted]	14.8 [redacted]
Pediatric Patients (N=3)		
	3.7 ± 5.2 [redacted]	13.5 ± 12.3 [redacted]
Patients Treated with One Patch, 4x daily		
Mean SD	9.8 ± 16.5 (24)	15.8 ± 16.4 (N=24)
Median (Range)	5.6 [redacted]	11.5 [redacted]
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 [redacted]	35.4 [redacted]
Patients Treated with Three Patches, 4x daily		
Mean SD	20.4 (N=2)	18.6 (N=2)
Median (Range)	20.4 [redacted]	18.6 [redacted]

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Amlexanox 2 mg Patch, DFS Copy

Table 6. Individual Serum Concentrations Patch Treatment Group Phase 3 Study AP-C-1U106

Patient ID	Pre Dose	2-hr post dose	
One Patch			
057	⌈		⌈
099			
100			
109			
141			
150			
151			
187			
261			
262			
263			
276			
277			
291			
327			
409			
657			
694			
697			
699			
719			
724			
277			
Two Patches			
063			
144			
335			
618			
619			
Three Patches			
058			
108	⌋		⌋

BQL=Below quantitation limit, ND=Not detected

Comments:

Prior to first dose on Day 4, the maximum pre-dose concentrations (C_{min}) were ⌋ and ⌋ ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 concentrations were ⌋ ng/mL. The inter-subject variability was high in all groups. Furthermore, because of low number of subjects in the 2 and 3 patch-treatment group, a dose-dependency could not be established.

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Amlexanox 2 mg Patch, DFS Copy

The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL. The reported C_{max} value for the approved amlexanox product 5% paste is 116 ±71.2 ng/mL (please see Table below).

Due to smaller sampling size, with two patch (N=5) and three (N=2) patch treatments with OraDisc, no conclusive observation on the systemic observation could be inferred.

In study no. BD34,787-110 submitted as part of the NDA 20-511 for the approved Aphthasol 5% oral paste, the following PK characteristics have been reported (N=12, adult population).

Parameter	Adult Mean ±SD (N=12)
Auc ₀₋₈ (ng·h/mL)	423.2 ±261.0
Auc _{0-inf} (ng·h/mL)	615.0 ±345.9
C _{max} (ng/mL)	116 ±71.2
T _{max} (hr)	2.55 ±0.82
Ke	0.215 ± 0.111
t _{1/2}	3.98 ± 1.84

Adverse Events in Patients: There were 96 reports of untoward application site reactions reported by 82 patients, 38 patients in the amlexanox patch group (12.5%) and 44 patients in the vehicle group (14.6%). All application-site events but 3 were deemed potentially related to application of the patches. Pain (reported by 51 patients) and burning (reported by 17 patients) were the most frequent and were reported with similar frequencies in the amlexanox patch and vehicle patch groups. Detail description of the AEs are provided in Tables 13-4, 13.5 and 13-6, page 77, Section 5.3.5.1, Vol 3 of this NDA submission).

Adverse Events in Pediatric Patients: Five patients in the amlexanox (13.5%) and 5 (10.2%) in the vehicle patch groups exhibited untoward application site reactions. All application-site reactions were deemed potentially related to application of the patches and rated as mild. Pain (3 patients) and paresthesia (4 patients) were the most frequent AEs. Eleven pediatric patients reported 14 AEs other than application site reactions. No type or events appeared to be more frequent in the amlexanox group than in the vehicle group.

Study No. AP-C-9E03: A phase 2/3 investigator-blind, randomized, parallel-group study to determine the effects and serum levels of amlexanox disc 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle discs or no treatment in patients 12 years of age or older. In this study the Early Formulation patch was applied qid for 7 days. Serum levels of amlexanox was determined after 3 dull days of treatment before the first application and 1 hour post-dosing on Day 4. The results of this study are summarized in the Table below. As agreed upon between the Sponsor and Agency, the above study AP-C-9E03 is not being considered for approval of this NDA. The PK results from this study have been summarized in the QBR section 2.1 for supportive purpose only.

Sampling Time	Mean ±SD	Median	Range	N
Pre-dose (ng/mL)	54.1 57.0	46.3	[5]	19
1 hr post-dose	60.1 64.0	41.2	[5]	36

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After multiple dosing for at least 3 days, most subjects have low serum levels of amlexanox pre-dose. The serum levels at 1-hr post-dose were similar to the pre-dose levels, suggesting slow absorption probably through the gastrointestinal tract rather than mostly through the oral mucosa of aphthous ulcer.

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4.3 Cover Sheet and OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information about the Submission</i>				
	Information		Information	
NDA Number	21-727	Brand Name	OraDisc™A	
OCPB Division	DPE III, HFD 880	Generic Name	Amlexanox 2mg, Mucoadhesive Patch	
Medical Division	ODE V, HFD 540	Drug Class	Topical	
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Treatment <input type="checkbox"/> of aphthous ulcers in adults and adolescents 12 years of age or older (as proposed by the Sponsor).	
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Mucoadhesive Patch	
Type of Submission	Original Submission	Strength	2 mg	
Related NDAs/ANDAs/INDs	IND 59,949	Route of Administration	Topical administration to the oral mucosa	
Date of Submission	Dec 09, 2003	Dosing Regimen	Four times daily after breakfast, lunch, dinner and <input type="checkbox"/> before bedtime. In case of multiple ulcers, apply one patch to each ulcer.	
Estimated Due Date of OCPB Review	Jun 09, 2004	Sponsor	Access Pharmaceuticals, Inc. Dallas, TX 75207-2107	
PDUFA Due Date	Oct 08, 2004	Priority Classification		
Division Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				

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Reference Bioanalytical and Analytical Methods	X			HPLC, LLOQ [] ng/mL, Range [] ng/mL []
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) - Healthy Volunteers-				
single dose in pediatric population:	X			<p><u>I. Study with Aphthasol Oral Paste 5%. Single Dose.</u> Study No. BD98-006: A phase 1 open label study in children to determine the pharmacokinetics of amlexanox after a single topical administration of 5 amlexanox paste % to the oral mucous membrane. N=12 healthy (6 males and 6 females) age 8-12 years, 105 to 120 mg of amlexanox of 5% paste. Serum Samples collected at pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose. Urine Samples collected at pre-dose, 0-6 hr, 6-12 hr and 12-24 hr.</p> <p>Determined with HPLC with LOQ [] ng/mL.</p>
multiple dose:				

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Patients-					
single dose:					<p>1. Study with New Formulation Single Dose. Protocol AP-C-1U107: A phase I study to investigate the pharmacokinetic characteristics of Amlexanox OraDisc 2 mg, in 18 subjects with minor Aphthous ulcers after a single application to 1-3 aphthous ulcers. N=18 (8 males, 10 females), age 18-63 (mean 36) <u>Criteria for Evaluation:</u> <u>Retention on Day 1</u>, at 0, 5, 15, 30, 45, 60, 75, 90 and 120 minutes after application <u>Resorption:</u> solid particle free in the oral cavity at any time yes/no <u>Pharmacokinetics:</u> Cmax, AUC0-24 and Tmax, also normalized for dose and body surface area:</p>
multiple dose:					
Dose proportionality -					
fasting / non-fasting single dose:					
fasting / non-fasting multiple dose:					
Drug-drug interaction studies -					
In-vivo effects on primary drug:					
In-vivo effects of primary drug:					
In-vitro:					
Subpopulation studies					
ethnicity:					
gender:	X				Pooled Data
pediatrics:		X			
geriatrics:					
renal impairment:					
hepatic impairment:					
PD:					
Phase 2:					
Phase 3:					
PK/PD:					
Phase 1 and/or 2, proof of concept:					

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Phase 3				<p>1. Study with New Formulation, Multiple Dose: Protocol AP-C-1U106: A phase 3 evaluator-blinded, randomized, parallel-group study to determine the effects the Amlexanox Mucoadhesive patch, OraDisc 2 mg on the healing of recurrent minor aphthous ulcers as compared with vehicle Mucoadhesive patches or no treatment. N=77 (for PK) at 7 clinical centers with 31 treated with OraDisc A patch. Treatment continues for 7 days or until all ulcers present at baseline healed. On day 4 of dosing, serum was collected before the first application and 2 hours after application.</p> <p>2. Study with Early Formulation Protocol AP-C-9E03: A phase 2/3 investigator-blinded, randomized, parallel-group study to determine the effects of Amlexanox disc, 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle or no treatment. PK objective to determine the serum levels of amlexanox after 3 full days of treatment with Early formulation N=137 (for PK) at 5 clinical centers. Treatment continues for 7 days or until all ulcers present at baseline healed, whichever occurred first. On day 4 of dosing, serum was collected before the first application and 1 hours after application.</p>
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution: In Vitro	X			<p>1. Study AP 03-10-01 to compare dissolution profile and delivery characteristics of Early Formulation and Final Formulation.</p>

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(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		5		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	YES	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • What are the properties of the formulation of the drug product? • What are the differences between Early Formulation (used in Phase I trials) and Final Formulation (used in Phase 3 trials)? • Are the dissolution profile of the Early and Final Formulation Comparables? • Are the active moieties in the serum appropriately identified and measured to assess pharmacokinetic parameters? • Are analytical methods sensitive enough to determine the extent of amlexanox absorption after topical buccal administration? • Can any meaningful result obtained from the pediatric pharmacokinetic study using Amlexanox 5% Oral Paste? • Is there a significant systemic absorption of amlexanox from the OraDisc 2 mg patch in the adults and adolescent (≥ 12 yrs of age) in the Phase 3 studies? 			
Other comments or information not included above	In addition to the above 4 PK studies (3 with OraDisc and 1 with amlexanox 5% paste in pediatrics), the Sponsor has cited PK results from the approved amlexanox 5% oral paste (NDA 20-511) and amlexanox oral tablets (12.5, 25, 50 and 100 mg, submitted in support of NDA 20-511).			
Primary reviewer Signature and Date	Chandra S. Chaurasia, Ph. D.			
Secondary reviewer Signature and Date	E. Dennis Bashaw, Pharm. D.			

Chandra S. Chaurasia, Ph.D.

Date: _____

Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

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RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

CC: NDA 21-727, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Chandra S. Chaurasia
9/2/04 09:48:56 AM
BIOPHARMACEUTICS

Arzu Selen
9/2/04 11:02:35 AM
BIOPHARMACEUTICS