

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Administrative/Correspondence Reviews

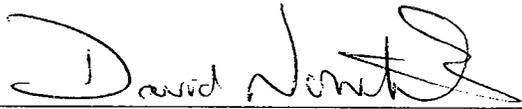
1.3.1 Patent Information

Access Pharmaceuticals, Inc., holds the following patents issued by the U.S. Patent and Trademark Office:

U.S. Patent No. 6,585,997; Moro et al. Mucoadhesive erodible drug delivery device for controlled administration of pharmaceuticals and other active compounds. Issued July 1, 2003, Expires August 16, 2021.

U.S. Patent No. 5,362,737; Vora et al. Methods of treating aphthous ulcer and other mucocutaneous disorders with amlexanox. Issued November 8, 1994, Expires July 19, 2013.

The under signed declares that Patent No.'s 6,585,997 and 5,232,637 cover the formulation, composition, and/or method of use of OraDisc™A, Amlexanox 2 mg, Mucoadhesive Patch. This product is the subject of this application for which approval is being sought.



David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

EXCLUSIVITY SUMMARY FOR NDA # 21-727 _____ SUPPL # _____

Trade Name TRADENAME Generic Name amlexanox

Applicant Name Access Pharmaceuticals HFD # 540

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / X /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an

esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / /
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-511 Aphthasol® 5% Oral Paste

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations

(other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

AP-C-1U106 (Pivotal); AP-C-9E03 (Supportive)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a

Study AP-C-1U106 (Pivotal)

Study AP-C-9E03 Supportive)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
Study AP-C-1U106

IND # 59,949 YES / X / ! NO / ___ / Explain: _____
!
!

Investigation #2
Study AP-C-9E03 (Supportive)

IND # 59,949 YES / X / ! NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES / ___ / Explain _____ ! NO / ___ / Explain _____
!
!
!
!
!
Investigation #2

YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/_/

If yes, explain: _____

Signature _____ Date _____
 Title: _____

Signature of Office/ _____ Date _____
 Division Director _____

Form OGD-011347 Revised 05/10/2004

cc:
 Archival NDA
 HFD- /Division File
 HFD- /RPM
 HFD-610/Mary Ann Holovac
 HFD-104/PEDS/T.Crescenzi

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-727 Supplement Type (e.g. SE5): _____ Supplement Number: _____

HFD-540 Trade and generic names/dosage form: OraDisc™ A (Amelexanox 2mg, Mucoadhesive Patch)

Applicant: Access Pharmaceuticals, Inc. Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of Aphthous Ulcers

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr 0 Tanner Stage _____
Max _____ kg _____ mo. 0 yr. 12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Impractical to use under age 12.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other:

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jacquelyn Smith, M.A.
Regulatory Project Manager

cc: NDA
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Fred Hyman

2/9/04 10:08:09 AM

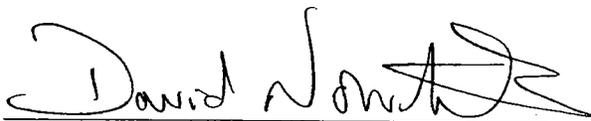
Fred Hyman is Acting Division Director today for Jonathan
Wilkin

1.3.8 Exclusivity Claims

OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch is the subject of this original New Drug Application. The active ingredient, amlexanox, has been previously approved by FDA for use in Aphthasol® (amlexanox oral paste) 5%, the subject of NDA 20-511.

Under IND# 59,949, Access Pharmaceuticals, Inc. has sponsored two safety and/or efficacy clinical trials with OraDisc™A (Study AP-C-1U106 and Study AP-C-2U108) that are “essential to the approval” of this application. Neither of these studies has been relied upon by the Agency to demonstrate the safety or efficacy of Aphthasol® (amlexanox oral paste) 5%. Furthermore, there are no published studies relevant to the safety and efficacy of the OraDisc™A drug product, and the publicly available data will not independently support approval of this New Drug Application.

Access Pharmaceuticals, Inc., hereby requests a three-year new dosage form exclusivity term for OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch as described in 21 CFR 314.108.



David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

1.3.2 Debarment Certification

Access Pharmaceuticals, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-727	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: TRADENAME (amlexanox) Mucoadhesive Patch, 2mg		Applicant: Access Pharmaceuticals
RPM: Jacquelyn Smith	HFD-540	Phone # 301-827-2020
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		October 8, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4675
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) N/A
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<ul style="list-style-type: none"> • This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 	
<ul style="list-style-type: none"> • OC clearance for approval 	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	() Verified (No FDA-3542a form submitted) Patent Statement was submitted.
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	N/A 21 CFR 314.50(i)(1)(i)(A) () Verified 21 CFR 314.50(i)(1) () (ii) () (iii)
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	() N/A (no paragraph IV certification) () Verified N/A () Yes () No N/A () Yes () No N/A () Yes () No

<p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (5).</i></p> <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	<p>N/A</p> <p>() Yes () No</p> <p>N/A</p> <p>() Yes () No</p> <p>N/A</p>
<p>❖ Exclusivity (approvals only)</p>	<p style="background-color: #cccccc;"></p>
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<p>Exclusivity summary was in application. Please note: This a 505(b)(1) application.</p>
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<p>() Yes, Application # _____ (X) No</p>
<p>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p>	<p>N/A</p>

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Draft label to sponsor (9/16/04)
• Most recent applicant-proposed labeling	9-24-04
• Original applicant-proposed labeling	12-4-03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC(7-15-04); DMETS (8-13-04)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Draft label to sponsor (9/16/04)
• Applicant proposed	12-4-03
• Reviews	9-20-04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	No requests
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	August 20, 2001
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other (Guidance Meeting)	August 13, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Med. TL/ 9-24-04
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Clinical Information

❖ Clinical review(s) (indicate date for each review)	9-24-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	9-22-04 (from clinical review)
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/6/04
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	9/10/04
❖ Biopharmaceutical review(s) (indicate date for each review)	9/2/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No DSI inspection
• Bioequivalence studies	No DSI inspection

CMC Information

❖ CMC review(s) (indicate date for each review)	9-24-04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	9-24-04
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: 9/14/04 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested

Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	8/6/04
❖ Nonclinical inspection review summary	No
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	No
❖ CAC/ECAC report	No

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appears This Way
On Original**



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5**

FACSIMILE TRANSMITTAL SHEET

Date: September 24, 2004

To: Amy Campbell, Manager, Regulatory Affairs/ David Nowotnik, Ph.D., Sr. VP, R & D	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/ (Amlexanox) Revised Draft Labeling	

Total no. of pages including cover: 7

Comments: If you agree with the proposed labeling, please fax us a statement confirming that you agree.
Thank you,
Jacquelyn

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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6 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NDA 21-727
N-000



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 21, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727 (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 3	

Document to be mailed: YES NO

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NDA 21-727
N-000

FDA Fax Memo

Date: September 21, 2004

Dear Ms. Campbell:

The clinical pharmacology and biopharmaceutics review team has asked that the following comment be conveyed to you.

With regards to in vitro dissolution, the Agency requests you to set an interim dissolution specification of NLT(Q) ζ J of the labeled content of the drug to be dissolved in 60 minutes.

Regards,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

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

/s/

Jacquelyn Smith
9/21/04 11:46:44 AM
CSO



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

ORIGINAL

N-000 (B2)
ORIG AMENDMENT

www.accesspharma.com
e-mail: akc@accesspharma.com

September 20, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

RECEIVED
SEP 21 2004
MEGA/CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 9

Re: Response to CMC Deficiencies, dated September 13, 2004, and to Labeling Comments in faxes dated August 16, and September 16, 2004

Dear Sir or Madam:

Reference is made to your faxes dated August 16, 2004, September 13, 2004, and September 16, 2004, in which a set of comments were made by the division.

Included in this submission please find the following:

- Response to CMC Deficiencies fax dated September 13, 2004
- Response to Labeling Comments in faxes dated August 16, 2004 and September 16, 2004

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 9/20/04
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDisc™A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Amlexanox.	CODE NAME (If any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical
(PROPOSED) INDICATION(S) FOR USE: Treatment of Aphthous Ulcers		

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION new dosage form for the treatment of aphthous ulcers
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. See attached List
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) IND # 59.959: Amlexanox OraDisc DMF # [redacted] DMF # [redacted] DMF # [redacted] DMF # [redacted]

RECEIVED
SEP 21 2004

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to CMC Reviewer Questions, Response to Labeling Comments, DMF Reference Letter

CERTIFICATION

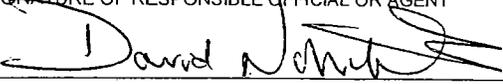
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 9/20/04
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	Telephone Number (214) 905-5100	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
ORDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBE# HFM-94
1241 Parklawn Dr., Room 3046
Rockville, MD 20852

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 16, 2004

To: Amy Campbell, Manager, Regulatory Affairs/ David Nowotnik, Ph.D., Sr. VP, R & D	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Revised Draft Labeling	

Total no. of pages including cover: 9

Comments: Please fax a highlight/strikeout copy, as well as a clean copy incorporating your suggested changes. A
con will be scheduled as soon as possible to discuss suggested changes.

Document to be mailed: YES NO

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Sept. 16, 2004

Attached is your proposed label for OraDisc, which includes suggested revisions that the Agency has made. Please review these changes. Also, please consider revision of the terms [] in line 82, and ' [] ' in line 98, as well as ' [] ' in line 100. Please propose a more consistent way to describe the disappearance of the disc.

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Food and Drug Administration
Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 14, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/9-3-04 Tcon	

Total no. of pages including cover: 5

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: September 3, 2004, 10:00 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: Amlexanox

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research and Development
Ric Zarzycki, Ph.D., Quality Control and Logistics
Amy Campbell, Manager, Regulatory Affairs

Phone: (214) 905-5100

Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
David Lin, Ph.D., Supervisor, Chemistry
Norman Schmuff, Ph.D., Acting Deputy Division Director
Felecia Curtis, Regulatory Health Project Manager
Jacquelyn Smith, Regulatory Health Project Manager

SUBJECT: NDA 21-727

A FDA-initiated telecon was held to discuss CMC issues related primarily to dissolution issues arising from the five FAXs from Access sent 8/31/2004. Following are FDA's questions/requests and the firm's responses:

-Why was USP dissolution metric of General Chapter <711> not employed?

--Access responded that they did not know, as this decision was made before participants joined the firm.

-Explain the [] for product

--Access concluded that there was an error in 8/31/2004 FAX 4 of 5, which inadvertently [] They agreed to FAX the corrected data.

-Explain why [] for lots 4257, 4258, and 4259 are []

--An investigation is currently underway to determine the cause of this.

-Why was the USP metric for Uniformity of Dosage Units <905> not employed?
--Access responded that they did not know, as this decision was made before participants joined the firm.

FDA indicated that compliance with the two indicated USP chapters would be included in a forthcoming CMC information request.

Addendum:

The corrected dissolution data was received today, September 3, 2004.

The conversation ended amicably.

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/s/

Norman Schmuff
9/14/04 06:47:37 AM

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/s/

Jacquelyn Smith
9/14/04 09:13:47 AM
CSO

NDA 21-727
N-000



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 13, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727 (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 4	

Document to be mailed: YES NO

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- c. A content uniformity attribute as per USP 27 < 905> Uniformity of Dosage Units.
 - d. Module 2 Volume 1.1 Section 2.3.P.5.1 contains a misprint in the specification, whereby the specification for [] content and dissolution is incorrectly stated. In this regard, the dissolution specification should indicate [] for Amlexanox Released in 60 min.; the specification for [] should indicate []
 - e. The use of the USP 27 < 711> metric for dissolution testing, including the acceptance criteria for S₁, S₂, and S₃ stages.
 - f. A discrepancy was reported in COAs specification for [] (see Module 3 Volume 1.4 Section 3.2P.5.4.1), whereby a value of NMT [] was reported instead of [] as shown in Table 2.3.P.5-1 specification.
- 6) Under the Analytical Procedures for OraDisc™ A, Amlexanox 2 mg Patch (2.3.P.5.2), the following information should be submitted:
- a. System suitability for the HPLC method.
 - b. A correction of the discrepancy for test methods [] which are reported as dissolution and content (assay), respectively in table 2.3.5.1 and as the reverse in the validation report.
- 7) Under Stability for OraDisc™ A, Amlexanox 2 mg Patch (2.3.P8), the following information should be submitted:
- a. Ongoing stability data [] when available.
 - b. An explanation for why [] Was an investigation conducted?

Regards,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

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

/s/

Jacquelyn Smith
9/13/04 03:07:28 PM
CSO

MEMORANDUM OF TELECON

DATE: September 3, 2004, 10:00 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: Amlexanox

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research and Development
Ric Zarzycki, Ph.D., Quality Control and Logistics
Amy Campbell, Manager, Regulatory Affairs

Phone: (214) 905-5100

Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
David Lin, Ph.D., Supervisor, Chemistry
Norman Schmuff, Ph.D., Acting Deputy Division Director
Felecia Curtis, Regulatory Health Project Manager
Jacquelyn Smith, Regulatory Health Project Manager

SUBJECT: NDA 21-727

A FDA-initiated telecon was held to discuss CMC issues related primarily to dissolution issues arising from the five FAXs from Access sent 8/31/2004. Following are FDA's questions/requests and the firm's responses:

-Why was USP dissolution metric of General Chapter <711> not employed?

--Access responded that they did not know, as this decision was made before participants joined the firm.

-Explain the [

--Access concluded that there was an error in 8/31/2004 FAX 4 of 5, which inadvertently]

[They agreed to FAX the corrected data.

-Explain why : [

--An investigation is currently underway to determine the cause of this.]

-Why was the USP metric for Uniformity of Dosage Units <905> not employed?

--Access responded that they did not know, as this decision was made before participants joined the firm.

FDA indicated that compliance with the two indicated USP chapters would be included in a forthcoming CMC information request.

Addendum:

The corrected dissolution data was received today, September 3, 2004.

The conversation ended amicably.

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/s/

Norman Schmuff
9/14/04 06:47:37 AM

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/s/

Mary Jean Kozma Fornaro
12/9/03 10:09:33 AM



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

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SEP 01 2004

CDR / CDER

www.accesspharma.com
e-mail: akc@accesspharma.com

August 30, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

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SEP 02 2004

MEGA/CDER

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SEP 01 2004

CDR / CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 8

N-000(BC)
ORIG AMENDMENT

Re: Response to Chemistry Reviewer's Questions, dated August 24, 2004;
Method Validation for In-Process Amlexanox Content

Dear Sir or Madam:

Reference is made to your Fax dated August 24, 2004, in which a set of requests was made by the chemistry reviewer.

Included in this submission please find:

- Responses to the Chemistry Reviewer's questions in the Fax of August 24, 2004.
- Requested dissolution data for stability data submitted in the Interim Stability Report, []
- Final Method and Method Validation Report for the In-Process Amlexanox Content of the Mucoadhesive Paste.

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 8/30/04
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED SEP 01 2004 CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDisc TM A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Amlexanox	CODE NAME (if any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical

PROPOSED INDICATION(S) FOR USE:
Treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc

DMF # [redacted]
DMF # [redacted]
DMF # [redacted]

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SEP 02 2004

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to CMC Reviewer Questions

CERTIFICATION

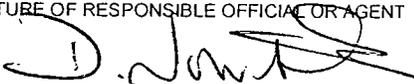
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 8/30/04
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107		Telephone Number (214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12425 Parklawn Dr., Room 3046
Rockville, MD 20852

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1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.	<input checked="" type="checkbox"/>
Address	2600 Stemmons Freeway Suite 176 Dallas, TX 75207-2107	
Contact	Ric Zarzycki, Ph.D. Director of Quality	
Phone	(214) 905-5100	
Activities at site	Finished product release testing, finished product stability testing	
Inspection readiness	Ready for Inspection	<input checked="" type="checkbox"/>

NDA 21-727

N-000



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: August 24, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 3	

Document to be mailed: YES NO

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ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

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SEP 01 2004

CDR / CDER

www.accesspharma.com
e-mail: akc@accesspharma.com

August 30, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

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SEP 02 2004

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SEP 01 2004

CDR / CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 8

N-000(BC)
ORIG AMENDMENT

Re: Response to Chemistry Reviewer's Questions, dated August 24, 2004;
Method Validation for In-Process Amlexanox Content

Dear Sir or Madam:

Reference is made to your Fax dated August 24, 2004, in which a set of requests was made by the chemistry reviewer.

Included in this submission please find:

- Responses to the Chemistry Reviewer's questions in the Fax of August 24, 2004.
- Requested dissolution data for stability data submitted in the Interim Stability Report, []
- Final Method and Method Validation Report for the In-Process Amlexanox Content of the Mucoadhesive Paste.

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

NDA 21-727
N-000

FDA Fax Memo

Date: August 24, 2004

Dear Ms. Campbell:

Chemistry has asked that the following comments be conveyed to you.

1) The proposed tentative expiration of 12 months at 25 deg C is acceptable provided that a cautionary statement against prolonged exposure at or above 30 deg C is added to the labeling. All of the labeling should be revised to include the following information:

Store at 25 deg C (77 deg F)

[Caution: Avoid prolonged exposure to temperatures above 30 deg C]

2) The storage statement of indicating suggested storage at [] is not acceptable both because of reasons stated above, and because no stability data were submitted to support refrigerated conditions. In this regard, please submit a revised stability protocol, and the data derived from these stability studies to support refrigerated conditions. All tests attributes as submitted under the Interim Stability Testing Report, [] dated 7/25/03 should also be included in the revised stability protocol.

3) Please submit individual tests results (i.e. the per cent dissolved for each individual unit, and the number of units tested) for the dissolution studies described in the Interim Stability Testing Report, [] dated 7/25/03 for Amlexanox OraDisc, 2 mg, Lot # 4257, 4258 and 4259.

Please respond as soon as possible. If you have any questions, please contact me at 301-827-2027.

Sincerely,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

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

/s/

Jacquelyn Smith
8/24/04 02:12:33 PM
CSO

NDA 21-727
N-000



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5**

FACSIMILE TRANSMITTAL SHEET

Date: August 16, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/Tradename comments	

Total no. of pages including cover: 7

Comments: Please find below comments regarding TRADENAME "OraDisc A".

Document to be mailed: YES NO

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FDA Fax Memo

DMETS does not recommend the use of the proprietary name OraDisc A. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Orudis KT. Include only the names that had the potential for confusion.

A. Look-Alike/Sound-Alike Issues

1. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).¹ Studies such as this one support DMETS' concern that healthcare professionals may omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.



¹ Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med. 2002;17:579-87.

2. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'l' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as directed." Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.

Handwritten script of the name 'OraDisc' in cursive, showing the 'D' and 'isc' parts.Handwritten script of the name 'Oralone' in cursive, showing the 'one' part.

3. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.

B. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation.

Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage form is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

C. Labeling, Packaging, and Safety Related Issues:

In the review of the container labels, carton and insert labeling of OraDisc A, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

- a. Some of the letters (e.g. 'Di') in the proprietary name appear too close together (see below), making it difficult to read. Additionally, the different shades of boxing used around the name dissect the letter 'A' of 'Ora' in half, making the name difficult to read as well. Revise accordingly.



- b. Ensure the established name is at least one-half the size of the proprietary name.

2. INSERT LABELING

a. General Comments

Throughout the package insert, the medication is referred to in several different ways, (i.e. OraDisc A, Amlexanox OraDisc, and Amlexanox OraDisc A). Please use either the proprietary name (OraDisc A) or the established name (Amlexanox Patch) when referring to the medication in order to avoid confusion.

b. PRECAUTIONS – Information for Patients Subsection

i. Instruction Number 1:

- Instruct patients to wash their hands before applying OraDisc A.
- Patients are instructed to apply OraDisc A ζ before bedtime in order to, “avoid the possibility of aspiration of soft, food-like particles that may come loose...” However, the patch may take up to 80 minutes to dissolve. Please advise patients to apply OraDisc A at least 80 minutes (e.g. an hour and a half) before bedtime, in order to allow time for the patch to completely dissolve.

ii. Instruction Number 2:

- Indicate up to how many patches may be used at one time.

iii. Instruction Number 3:

- Instruct patients what to do if the patch does not adhere readily.

iv. Instruction Number 5:

- Specify what is meant by particles in the statement, “...to ensure that no particles come loose during sleep.”
- See second comment under Number 1.

NDA 21-727
N-000

- c. The information provided in the Precautions section, Information for Patients, must be reprinted at the end of the labeling per CFR 201.57(f)(2).
Revise accordingly.

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/s/

Jacquelyn Smith
8/16/04 01:24:43 PM
CSO



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

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AUG 17 2004

CDR/CDER

www.accesspharma.com
e-mail: alc@accesspharma.com

August 13, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

11-000(SU)

ORIG AMENDMENT

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 7

Re: 4-month Safety Update Report

Dear Sir or Madam:

Included in this submission please find the 4-month Safety Update Report. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The safety update is located in Module 1, Section 1.3.10.

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

4 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: akc@accesspharma.com

N-000(C)

June 8, 2004

Jonathon Wilkin, M.D.
Division of Dermatologic and Dental Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.,
Rockville, MD 20850

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JUN 09 2004
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LETTER OF AUTHORIZATION

NDA 21-727
OraDisc A, 2mg Mucoadhesive Patch
Volume: N/A – general correspondence

NEW CORRESP

Dear Dr. Wilkin,

In reference to a recent telephone call from Ms. Jacquelyn Smith to Access, Access Pharmaceuticals authorizes the agency to use any information contained in NDA 20-511, Aphthasol[®], 5% Oral Paste, in the agency's review of NDA 21-727, OraDisc A, 2mg Mucoadhesive Patch.

Sincerely,

David P. Nowotnik, Ph.D.
Snr. V.P., Research & Development



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: akc@accesspharma.com

June 2, 2004

Jonathon Wilkin, M.D.
Division of Dermatologic and Dental Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.,
Rockville, MD 20850

LETTER OF AUTHORIZATION

NDA 21-727
OraDisc A, 2mg Mucoadhesive Patch
Volume: N/A – general correspondence

Dear Dr. Wilkin,

In reference to the telephone call earlier today to Access by Ms. Jacquelyn Smith, Access Pharmaceuticals authorizes the use of the chemistry, manufacturing and controls information in NDA 20-511, Aphthasol[®], 5% Oral Paste, in the agency's review of NDA 21-727, OraDisc A, 2mg Mucoadhesive Patch.

If you have any further requests, or require any additional information, please do not hesitate in contacting me.

Sincerely,

David P. Nowotnik, Ph.D.
Snr. V.P., Research & Development



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5**

FACSIMILE TRANSMITTAL SHEET

Date: June 1, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 5/28/04 tcon	

Total no. of pages including cover: 4

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: May 28, 2004, 9:35 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: Amy L. Campbell, Manager, Regulatory Affairs
Christiane M. Baud, Ph.D., Vice President, Clinical Development

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, D.D.S., M.B.A, Dental Team Leader
Frederick Hyman, D.D.S., M.P.H., Dental Officer
Jacquelyn Smith, Regulatory Project Manager

The FDA contacted the Sponsor regarding their NDA submission that is currently under review, including their submission of April 16, 2004 in which [

_____]The Agency said 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. The review will proceed and if the Agency requires additional information, it will contact the Sponsor.

The conversation ended amicably.

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this page is the manifestation of the electronic signature.**

/s/

John Kelsey
5/28/04 02:45:27 PM

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

/s/

Jacquelyn Smith
6/1/04 08:39:14 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: May 17, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 050404 tcon	

Total no. of pages including cover: 4

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: May 4, 2004, 2:30 PM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, D.D.S., M.B.A, Dental Team Leader
Frederick Hyman, D.D.S., M.P.H., Dental Officer
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: New Protocol

In a teleconference, on March 26, 2004, the Agency requested that the Sponsor propose a C

..... J This study would involve a
C J. The
Sponsor stated that a complete clinical study plan for the clinical study would be submitted
within two weeks. The Sponsor submitted this new protocol to the Agency on April 16, 2004.

In today's teleconference, the Agency requested more time to review the protocol. The Sponsor agreed to the Agency's request since the Sponsor is not ready to begin the clinical study.

The conversation ended amicably.

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

/s/

John Kelsey
5/17/04 02:22:26 PM

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

/s/

Jacquelyn Smith
5/17/04 02:36:45 PM
CSO



ACCESS
PHARMACEUTICALS, INC.

ORIGINAL

RECEIVED
MAR 26 2004
CDR / CDER

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

March 24, 2004

N-600(Bm)
ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

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MAR 29 2004
DDR-110 / CDER

RECEIVED
MAR 29 2004
MEGA/CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 6

Re: Response to Clinical Reviewer's Question, dated March 22, 2004

Dear Sir or Madam:

Reference is made to your fax dated March 22, 2004, in which a question about patient enrollment was made by the clinical reviewer.

Included in this submission please find the response to the Clinical Reviewer's question in the fax of March 22, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The response is located in Module 1 as listed in Section 1.2 "Submission Volume 6 Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 3/24/04
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED MAR 26 2004 CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDisc TM A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Amlexanox	CODE NAME (If any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical
(PROPOSED) INDICATION(S) FOR USE: treatment of Aphthous Ulcers		

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION new dosage form for the treatment of aphthous ulcers
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. See attached List

RECEIVED
MAR 29 2004

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

RECEIVED
MAR 29 2004

CDR-116 / CDER

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Response to Clinical Reviewer Question dated March 22, 2004

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 		TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 3/24/04
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107		Telephone Number (214) 905-5100	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.	F
Address	2600 Stemmons Freeway	
	Suite 176	
	Dallas, TX 75207-2107	
Contact	Ric Zarzycki, Ph.D. Director of Quality	
Phone	(214) 905-5100	
Activities at site	Finished product release testing, finished product stability testing	
Inspection readiness	Ready for Inspection	J



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: March 22, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: 301-827-2075
Phone number: (214) 905-5100	Phone number: 301-827-2027
Subject: NDA 21-727/OraDisc	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

March 22, 2004

Dear Ms Campbell:

Per our discussion by telephone this morning, I am faxing this request for information from our review team with regard to NDA 21-727/OraDisc.

In the process of reviewing the data submitted with NDA 21-727, the Agency is evaluating not only trial 1U106, but the earlier clinical trials as well. In the process of review, we noticed that there were 7 investigators who participated in both studies 1U106 and 9E03. []

The patient enrollment for these investigators accounts for about 27.4% (192/701) and 49.6% (199/401) of the total enrollment in studies 1U106 and 9E03, respectively. Could you tell us how many of those 192 subjects in study 1U106 were also subjects in study 9E03?

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On Original



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

ORIGINAL

www.accesspharma.com
e-mail: AKC@accesspharma.com

N-900 (B2)
ORIG AMENDMENT

March 15, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

RECEIVED RECEIVED
MAR 16 2004 MAR 17 2004
CDR / CDER MEGA/CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 5

Re: Response to Clinical Reviewer's Questions, dated February 20, 2004

Dear Sir or Madam:

Reference is made to your Filing Review Letter dated February 20, 2004, in which a set of requests was made by the reviewers.

Included in this submission please find the responses to the Clinical and Biostatistics Reviewers' questions in the Filing Review Letter of February 20, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The response is located in Module 1 and the report is located in Module 5, as listed in Section 1.2 "Volume 5.1 Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Access Pharmaceuticals, Inc.

DATE OF SUBMISSION
3/15/04

RECEIVED

MAR 17 2004

TELEPHONE NO. (Include Area Code)
(214) 905-5100

FACSIMILE (FAX) Number (Include Area Code)
(214) 905-5101

MEGA/CDER

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

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MAR 16 2004

N-009 (132)
ORIG AMENDMENT

CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-727

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Amlexanox 2mg, Mucoadhesive Patch

PROPRIETARY NAME (trade name) IF ANY
OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)
Amlexanox

CODE NAME (if any)

DOSAGE FORM:
Mucoadhesive Patch

STRENGTHS:
2 mg

ROUTE OF ADMINISTRATION:
topical

PROPOSED INDICATION(S) FOR USE:

treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE
(check one)

- NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

- TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

Application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Answers to Clinical and Biostatistics Questions

CERTIFICATION

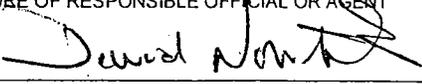
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 3/15/04
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176. Dallas. TX 75207-2107		Telephone Number (214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. If you have any comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.	T
Address	2600 Stemmons Freeway Suite 176 Dallas, TX 75207-2107	
Contact	Ric Zarzycki, Ph.D. Director of Quality	
Phone	(214) 905-5100	
Activities at site	Finished product release testing, finished product stability testing	
Inspection readiness	Ready for Inspection	J



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

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MAR 01 2004
CDR/CDER

RECEIVED
MAR 02 2004
MEGA/CDER

www.accesspharma.com
e-mail: AKC@accesspharma.com

February 27, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Recode N-000) SE
PER P11 3-5-04
N-000 (BE)(BZ)
ORIG AMENDMENT

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 4

Re: Response to Chemistry Reviewer's Questions, dated February 20, 2004

Dear Sir or Madam:

Reference is made to your Filing Review Letter dated February 20, 2004, in which a set of requests was made by the reviewers.

Included in this submission please find the responses to the Chemistry Reviewer's questions in the Filing Review Letter of February 20, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

N 000 (BZ)

APPLICANT INFORMATION

NAME OF APPLICANT
Access Pharmaceuticals, Inc.

DATE OF SUBMISSION
2/27/04

ORIG AMENDMENT

TELEPHONE NO. (Include Area Code)
(214) 905-5100

FACSIMILE (FAX) Number (Include Area Code)
(214) 905-5101

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

RECEIVED RECEIVED

MAR 02 2004

MAR 01 2004

MEGA/CDER CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Amlexanox 2mg, Mucoadhesive Patch

PROPRIETARY NAME (trade name) IF ANY
OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
Amlexanox

CODE NAME (If any)

DOSAGE FORM:
Mucoadhesive Patch

STRENGTHS:
2 mg

ROUTE OF ADMINISTRATION:
topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE (check one)
 NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ND # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) EA Waiver Information, Response to CMC Reviewer Questions

CERTIFICATION

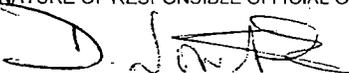
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 2/27/04
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	Telephone Number (214) 905-5100	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: February 20, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: 301-827-2075
Phone number: (214) 905-5100	Phone number: 301-827-2027
Subject: NDA 21-727/OraDisc filing review letter	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

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FILING REVIEW LETTER

NDA 21-727

Access Pharmaceuticals, Inc.
Attention: David P. Nowotnik, Ph.D.
Senior VP, Research & Development
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

Dear Dr. Nowotnik:

Please refer to your December 4, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for, OraDisc™ A (amlexanox) Mucoadhesive Patch, 2mg.

We also refer to your submissions dated December 12, 2003, January 8 and 30, 2004 and February 3, 2004.

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 6, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. No environmental assessment or request for categorical exclusion has been provided.
2. We cannot locate data requested by the Division during the IND phase & pre-NDA meeting.
3. We cannot locate the Investigational Formulations information.
4. Desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector cannot be located and have been requested.

Clinical:

1. In Study AC-P-1U106, your reported results for the primary outcome variable show a statistically significant improvement on Day 5. However, at Day 7 this trend reversed.
2. In Study AC-P-1U106, the secondary endpoint, pain relief, shows no statistically significant improvement in the OraDisc at Day 5, or at any other day compared to vehicle patch.

Biostatistics:

1. There are no subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

We request that you submit the following information to address the potential review issues described above:

Chemistry, Manufacturing and Controls:

1. Please provide an environmental assessment or, if you intend to request a categorical exclusion, please provide the calculations to support the categorical exclusion.
2. Please identify where all data requested by the division during the IND phase & pre-NDA meeting can be found in the NDA.
3. Please indicate where the Investigational Formulations information can be found in the NDA.
4. Please forward desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector, as requested by telephone on February 17, 2004.

Clinical:

1. Please provide any explanation for why the trend for the primary outcome variable reverses on Day 7, with the vehicle patch showing a better outcome than the OraDisc.
2. Please provide any rationale for not seeing an improvement in pain scores.

Biostatistics:

1. For each of studies 1U106 and 9E03, please submit subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-727

Page 3

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

Stanka Kukich

2/20/04 01:58:29 PM

Sign off for Dr. Jonathan Wilkin, Division Director

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: February 13, 2004	DESIRED COMPLETION DATE: July 19, 2004 PDUFA DATE : October 8, 2004	ODS CONSULT #: 04-0048
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TO: Jonathan Wilikin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Jacquelyn Smith
Project Manager
HFD-540

PRODUCT NAME: Oradisc™ A (Amlexanox Patch) 2 mg NDA#: 21-727	NDA SPONSOR: Access Pharmaceuticals, Inc.
--	--

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, OraDisc™ A.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name OraDisc acceptable from a promotional perspective.
4. DMETS recommends contacting Dr. Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC) regarding the established name of OraDisc™ A.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 7, 2004
NDA#: 21-727
NAME OF DRUG: OraDisc™ A (Amlexanox Patch) 2 mg
NDA HOLDER: Access Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for assessment of the proprietary name, OraDisc™ A, regarding potential name confusion with other proprietary and/or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION

OraDisc™ is a mucoadhesive patch that contains 2 mg of amlexanox per patch. Amlexanox is indicated for the treatment of [] aphthous ulcers in adults and adolescents 12 years of age and older. OraDisc™ A should be applied to the ulcer as soon as possible after first noticing the symptoms of an aphthous ulcer and should be used four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and [] before bedtime. In case of multiple ulcers, apply one patch to each ulcer. OraDisc™ A is supplied in bottles of 20 patches.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to OraDisc™ A to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tndb/index.html>.

was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name OraDisc A. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name OraDisc A acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with OraDisc A. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
OraDisc A	Amlexanox Mucoadhesive Patch 2 mg	One patch on each ulcer four times daily	
Oraqix	Lidocaine/Prilocaine Periodontal Gel 2.5%/2.5%	Use topically during dental procedures	SA
Orudis KT	Ketoprofen Tablets 12.5 mg	12.5 mg to 25 mg by mouth every 4 to 6 hours.	SA/LA
Oralone	Triamcinalone Acetonide Dental Paste 0.1%	Apply a small amount of paste to affected area two to three times daily	LA
Orabase	gelatin, pectin and sodium carboxymethylcellulose in Plastibase Paste	Apply a small amount of paste to affected area as needed.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

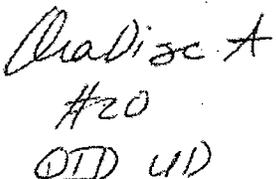
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to OraDisc A were discussed by the Expert Panel (EPD).

C. PREScription ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of OraDisc A with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for OraDisc A (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>“The first prescription is for OraDisc A. Use 4 times a day as directed. Number 20...”</p>
<p>Inpatient RX:</p> 	

2. Results:

One respondent interpreted the proposed name as Orudis A. Orudis A sounds and looks similar to the currently marketed product Orudis KT.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name OraDisc A, the primary concerns related to look-alike and sound-alike confusion with Orudis KT, Oralone, Orabase HCA, and Oraqix.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, one respondent from the verbal study misinterpreted the product as Orudis A, which sounds and looks similar to the currently marketed product, Orudis KT. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, OraDisc A.

1. Sound-Alike and Look-Alike Concerns

- a. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).⁵ Studies such as this one support DMETS' concern that healthcare professionals may omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.



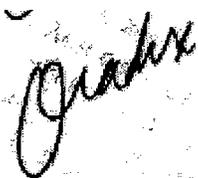
- b. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'I' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as

⁵ Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med. 2002;17:579-87.

directed.” Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.



- c. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.
- d. OraDisc A can look similar to Orabase when scripted. Orabase is a plasticized hydrocarbon gel that is a component of several OTC products. Such products include Orabase B, Kenalog with Orabase, Orabase Baby Teething Gel, Orabase Lip Healing Gel, and Orabase with Benzocaine, and Orabase HCA. Orabase is a protective paste used to protect and soothe any sore and painful areas in the mouth or on the gums, including ulcers, sore spots from dentures, and toothbrush injury and to protect the skin around ileostomies, colostomies, fistulas and ileal conduits. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Orabase both begin with 'Ora' and contain seven letters, which are the principal contributions to the look-alike characteristics of the names. Additionally, the upstrokes in each name ('d' vs. 'b') occur in the same position and can look similar depending on how they are scripted. In addition, the last two letters of the names ('sc' vs. 'se') can also look similar when scripted. Furthermore, both products would be applied to the affected areas of the mouth, several times a day (four times daily vs. as needed), while the condition being treated persists. While plain Orabase can be ordered alone, it is most often used in conjunction with another product such as Kenalog in Orabase, or Orabase with Benzocaine. If plain Orabase were prescribed, the pharmacist would have to call the prescriber and clarify the order to determine which product to dispense. Therefore, the necessity for the use of a modifier to correctly dispense Orabase helps to distinguish OraDisc A from Orabase enough to decrease the potential for medication errors due to name confusion.



2. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation.

Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage form is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name OraDisc A. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Orudis KT. Include only the names that had the potential for confusion.

A. Look-Alike/Sound-Alike Issues

1. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).⁶ Studies such as this one support DMETS' concern that healthcare professionals may omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The

⁶ Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.



2. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'l' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as directed." Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.



3. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.

B. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation.

Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage form is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

C. Labeling, Packaging, and Safety Related Issues:

In the review of the container labels, carton and insert labeling of OraDisc A, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

- a. Some of the letters (e.g. 'Di') in the proprietary name appear too close together (see below), making it difficult to read. Additionally, the different shades of boxing used around the name dissect the letter 'A' of 'Ora' in half, making the name difficult to read as well. Revise accordingly.



- b. Ensure the established name is at least one-half the size of the proprietary name.

2. INSERT LABELING

a. General Comments

Throughout the package insert, the medication is referred to in several different ways, (i.e. OraDisc A, Amlexanox OraDisc, and Amlexanox OraDisc A). Please use either the proprietary name (OraDisc A) or the established name (Amlexanox Patch) when referring to the medication in order to avoid confusion.

b. PRECAUTIONS – Information for Patients Subsection

i. Instruction Number 1:

- Instruct patients to wash their hands before applying OraDisc A.

- Patients are instructed to apply OraDisc A \bar{C}] before bedtime in order to, “avoid the possibility of aspiration of soft, food-like particles that may come loose...” However, the patch may take up to 80 minutes to dissolve. Please advise patients to apply OraDisc A at least 80 minutes (e.g. an hour and a half) before bedtime, in order to allow time for the patch to completely dissolve.
- ii. Instruction Number 2:
 - Indicate up to how many patches may be used at one time.
- iii. Instruction Number 3:
 - Instruct patients what to do if the patch does not adhere readily.
- iv. Instruction Number 5:
 - Specify what is meant by particles in the statement, “...to ensure that no particles come loose during sleep.”
 - See second comment under Number 1.
- c. The information provided in the Precautions section, Information for Patients, must be reprinted at the end of the labeling per CFR 201.57(f)(2). Revise accordingly.

Appears This Way
On Original

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name OraDisc™ A.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
- C. DDMAC finds the proprietary name OraDisc A acceptable from a promotional perspective.
- D. DMETS recommends contacting Dr. Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC) regarding the established name of OraDisc™ A.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A

Inpatient Written	Outpatient Written	Verbal
Ora Disc A	CliaDisc A	Oradisc A
OraDisc	Ora Disc A	Oradisc A
Oradisc A	Ora Disc A	Oradisc A
OraDisc A	OraDisc A	Oradisc A
Oradisc A	Oradisc A	Oradisc A
OraDisc A	Oradisc A	OraDisc A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
OraDisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	OraDiskA
OraDisc A	OraDisc A	Oradisk-A
OraDisc A	Oradisc A	Orgis A
OraDisc A	Oradisc A	Orgis-A
Oradisc A	OraDisc A	Orudis-A
OraDisc A		
Oradisc A		
Oradisc A		
Oradix A		
OraDix A		

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

/s/

Kristina Arnwine
8/13/04 03:00:00 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/13/04 03:22:38 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/13/04 03:34:23 PM
DRUG SAFETY OFFICE REVIEWER



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

RECEIVED
FEB 04 2004
MEGA/CDER

www.accesspharma.com
e-mail: AKC@accesspharma.com

February 3, 2004

Jacquelyn Smith, Project Manager, Room N-236
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

N-000 (BZ)

ORIG AMENDMENT

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727

Re: Submission of Clinical Study Protocols and Labeling in Word Format

Dear Ms. Smith:

As you requested, please find a desk copy on CD-ROM of the Amlexanox OraDisc clinical study protocols and draft labeling files in Word format. Included on this CD-ROM are:

- Study AP-C-1U106: Protocol and Amendment
- Study AP-C-1U107: Protocol and Amendments
- Study AP-C-2U108: Protocol
- Study AP-C-9E03: Protocol and Amendments
- Study AP-C-9E02: Protocol and Amendments
- Study AP-C-9E01: Protocol
- Study AP-C-9U05: Protocol and Amendment
- Draft Label
- Draft Insert.

If you have any questions, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:

Jacquelyn Smith
Project Manager
Division of Dermatologic and Dental Drug Products

DATE: February 12, 2004

IND NO.

NDA NO. 21-727

TYPE OF DOCUMENT

New NDA

DATE OF DOCUMENT:

December 4, 2003

NAME OF DRUG:

OraDisc™ A (Amlexanox 2mg,
Mucoadhesive Patch)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:

3S

DESIRED COMPLETION DATE:

Labeling mtg. is July 19, 2004

NAME OF FIRM: Access Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the requested tradename "OraDiscTMA." The package insert and bottle label is attached. I will also send a hard copy. Labeling meeting is scheduled for July 19, 2004.

PDUFA DATE: October 8, 2004

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Drug Risk Evaluation (DDRE), HFD-430
(Room 15B-08, PKLN Bldg.)

FROM:
Jacquelyn Smith
Project Manager
Division of Dermatologic and Dental Drug Products

DATE: February 12, 2004

IND NO.

NDA NO. 21-727

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT:
December 4, 2003

NAME OF DRUG:
OraDisc™ A (Amlexanox 2mg,
Mucoadhesive Patch)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
3S

DESIRED COMPLETION DATE:
Labeling mtg. is July 19, 2004

NAME OF FIRM: Access Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The package insert and bottle label is attached. I will also send a hard copy. Labeling meeting is scheduled for July 19, 2004.

PDUFA DATE: October 8, 2004

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
x MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Division of Drug Marketing, Advertising and Communications, HFD-42 PKLN Room 17B04		FROM: Jacquelyn Smith Project Manager Division of Dermatologic and Dental Drug Products		
DATE: February 12, 2004	IND NO.	NDA NO. 21-727	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT: December 4, 2003
NAME OF DRUG: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: Labeling mtg. is July 19, 2004
NAME OF FIRM: Access Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
The package insert and bottle label is attached. I will also send a hard copy. Labeling meeting is scheduled for July 19, 2004.				
PDUFA DATE: October 8, 2004				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) x <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Jacquelyn Smith
2/13/04 08:20:06 AM



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

ORIGINAL

N-000(BS)
ORIG AMENDMENT

January 30, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

RECEIVED

FEB 02 2004

RECEIVED CDR/CDER

FEB 03 2004

MEGA/CDER -000- BS

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 3

Re: Submission of SAS Datasets

Dear Sir or Madam:

Per the request of the DDDDP, please find the submission of SAS Datasets for studies AP-C-1U106 and AP-C-9E03 in the SAS transport format. Included on this CD-ROM are:

- Electronic copies of this cover letter and FDA Form 356h in pdf format;
- Study AP-C-1U106: SAS dataset in SAS transport format; and
- Study AP-C-9E03: SAS dataset in SAS transport format.

If you have any questions, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 1/30/04
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED FEB 02 2004 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDisc TM A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Amlexanox	CODE NAME (If any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical
(PROPOSED) INDICATION(S) FOR USE: treatment of Aphthous Ulcers		

RECEIVED
FEB 03 2004
MEGA/CDER

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION

new dosage form for the treatment of aphthous ulcers
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

D # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) SAS data sets for pivotal studies

CERTIFICATION

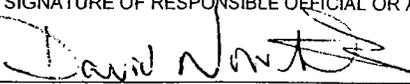
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 1-30-2004
--	---	--------------------

ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	Telephone Number (214) 905-5100
--	--------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Access Pharmaceuticals, Inc.
New Drug Application, Amlexanox Oradisc™, 2 mg

CONFIDENTIAL
Volume 3

3.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway Suite 176 Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Ready for Inspection

L

J



Food and Drug Administration
Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: January 29, 2004

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 012804 tcon	

Total no. of pages including cover: 5

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

MEMORANDUM OF TELECON

DATE: January 28, 2004, 12:30 PM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development
Amy L. Campbell, Manager, Regulatory Affairs
└ Biostatistics Consultant

Phone: (214) 905-5100

Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, DDS, M.B.A., Dental Team Leader
Mohamed Al-Osh, Ph.D., Team Leader, Biostatistics
Kathleen Fritsch, Ph.D., Biostatistician
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: NDA 21-727

To facilitate the review process, the following information was requested by the Division.

1. Please submit the complete electronic database in SAS transport format for Study AP-C-1U106. The database must contain all efficacy, safety, and background data from the CRFs, including baseline data and data from each visit. Per the annotated CRF, the relevant files for Study AP-C-1U106 appear to be INCLUS, EXCLUS, DEMOG, MEDH, ORAL-EXM, EXAM, SBSM, CONMED, DIARY_M, DIARY-P, ADVE, AND DRGR. Each file needs to contain the treatment assignments. The efficacy data sets should also include derived values for all primary and secondary endpoints and any other variables needed to conduct the primary and secondary analyses, such as ulcer size, and success endpoints. The submitted files (pops.xpt and logit.xpt) are insufficient for review, as they do not contain all of the efficacy, safety, and background data. Also, the Agency cannot review Study AP-C-9E03 unless Access submits the electronic database for Study AP-C-9E03.

Submit an official copy of the database to the NDA and a desk copy to Jacquelyn Smith before February 3, 2004.

2. Submit subgroup analysis results (tables and discussion) by gender, race, and age for the primary efficacy endpoints for Study AP-C-1U106. Submit the subgroup analyses to the NDA as soon as possible, but they may be submitted after February 9, 2004.

The Sponsor agreed to submit the information officially and submit a desk copy to Jacquelyn Smith before February 3, 2004.

Appears This Way
On Original

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

/s/

John Kelsey
1/28/04 02:58:59 PM

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

/s/

Jacquelyn Smith
1/29/04 07:54:23 AM
CSO



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

January 8, 2004

N-000(C)

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RECEIVED
JAN 12 2004
NEW CORRESP MEGA/CDER

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. N/A - Correspondence

Re: Corrected Cover Letter

Dear Dr. Wilkin:

The cover letter sent with the original submission of NDA 21-727, for Amlexanox 2mg, Mucoadhesive Patch, stated, in error, that the NDA was a 505(b)(2) submission. The letter should be corrected to read, as follows:

In accordance with 21 CFR 314.50, enclosed is an original 505(b)(1) New Drug Application for OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch). The required user fee was submitted on December 5, 2003. A copy of the CTD Quality Information (Module 1, Module 2, and Module 3) is being sent concurrently to the FDA District Office in Dallas, TX.

The facilities for the production of the drug product, [] will be available for inspection in late January, 2004 or any date thereafter. The facilities for the production of the drug substance, [] are ready for inspection.

We appreciate the reviews and discussion by your staff during the IND stage of the development of the product. If you have any questions or additional comments, please contact me at (214) 905-5100 or at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL



FILING REVIEW LETTER

NDA 21-727

2/20/04

Access Pharmaceuticals, Inc.
Attention: David P. Nowotnik, Ph.D.
Senior VP, Research & Development
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

Dear Dr. Nowotnik:

Please refer to your December 4, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for, OraDisc™ A (amlexanox) Mucoadhesive Patch, 2mg.

We also refer to your submissions dated December 12, 2003, January 8 and 30, 2004 and February 3, 2004.

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 6, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. No environmental assessment or request for categorical exclusion has been provided.
2. We cannot locate data requested by the Division during the IND phase & pre-NDA meeting.
3. We cannot locate the Investigational Formulations information.
4. Desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector cannot be located and have been requested.

Clinical:

1. In Study AC-P-1U106, your reported results for the primary outcome variable show a statistically significant improvement on Day 5. However, at Day 7 this trend reversed.
2. In Study AC-P-1U106, the secondary endpoint, pain relief, shows no statistically significant improvement in the OraDisc at Day 5, or at any other day compared to vehicle patch.

Biostatistics:

1. There are no subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

We request that you submit the following information to address the potential review issues described above:

Chemistry, Manufacturing and Controls:

1. Please provide an environmental assessment or, if you intend to request a categorical exclusion, please provide the calculations to support the categorical exclusion.
2. Please identify where all data requested by the division during the IND phase & pre-NDA meeting can be found in the NDA.
3. Please indicate where the Investigational Formulations information can be found in the NDA.
4. Please forward desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector, as requested by telephone on February 17, 2004.

Clinical:

1. Please provide any explanation for why the trend for the primary outcome variable reverses on Day 7, with the vehicle patch showing a better outcome than the OraDisc.
2. Please provide any rationale for not seeing an improvement in pain scores.

Biostatistics:

1. For each of studies 1U106 and 9E03, please submit subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-727

Page 3

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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

/s/

Stanka Kukich

2/20/04 01:58:29 PM

Sign off for Dr. Jonathan Wilkin, Division Director



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-727

2/13/04

Access Pharmaceuticals, Inc.
Attention: Amy Campbell
Manager, Regulatory Affairs
2600 Stemmons Freeway
Suite 176
Dallas, TX 75207-2107

Dear Ms. Campbell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: OraDisc (amlexanox) Mucoadhesive Patch, 2 mg

Review Priority: Standard (S)

Date of Application: December 4, 2003

Date of Receipt: December 9, 2003

Our Reference Number: NDA 21-727

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 6, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 9, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-727

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

MARY JEAN KOZMA-FORNARO
SUPERVISOR, PROJECT MANAGEMENT
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jacquelyn Smith
2/13/04 11:40:47 AM
Signed for Mary Jean Kozma-Fornaro

NDA 21-727
N-000



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: December 29, 2003

To: Amy Campbell, Manager, Regulatory Affairs	From: Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	Fax number: (301) 827-2075
Phone number: (214) 905-5100	Phone number: (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-727
N-000

FDA Fax Memo

Date: December 29, 2003

Dear Ms. Campbell:

We are unable to locate records for the following facilities through the Office of Compliance:

- Access Pharmaceuticals, Inc., 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207 [Finished Product Release Testing & stability testing]

- [REDACTED]

- [REDACTED]

Please confirm that these corporate names and addresses are correct and current. Copies of the most recent facilities registration form (FDA 2656) may be helpful in this respect.

Sincerely,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

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

/s/

Jacquelyn Smith
12/29/03 09:15:35 AM
CSO



ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

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DEC 15 2003

CDR/CDER

www.accesspharma.com
e-mail: AKC@accesspharma.com

December 12, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

RECEIVED

DEC 17 2003

MEGA/CDER

N-000(c)

NEW CORRESP

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 2

Re: Resubmission of Electronic Files

Dear Sir or Madam:

As requested in your fax dated 12/11/2003, please find the resubmission of the electronic files in the correct electronic formats. Included on this CD-Rom are:

- Electronic copies of this cover letter and FDA Form 356h in pdf format;
- Study AP-C-1U106: Annotated CRFs in pdf format, SAS dataset in SAS transport format, derived dataset specifications in pdf format;
- Study AP-C-9E03: Annotated CRFs in pdf format, SAS dataset in SAS transport format, derived dataset specifications in pdf format; and
- Bridging Analysis SAS transport format.

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 12/12/03
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED DEC 15 2003 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDisc TM A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Amlexanox	CODE NAME (if any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical

(PROPOSED) INDICATION(S) FOR USE:

treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b)(1)	<input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug	Holder of Approved Application	
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ND # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

RECEIVED

DEC 17 2003

MEGA/CDER

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
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<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) SAS data sets, electronic annotated CRFs

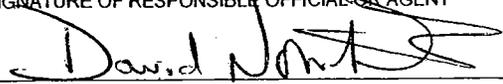
CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 12/12/03
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107		Telephone Number (214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CBER, HFM-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

2.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.	L
Address	2600 Stemmons Freeway Suite 176 Dallas, TX 75207-2107	
Contact	Ric Zarzycki, Ph.D. Director of Quality	J
Phone	(214) 905-5100	
Activities at site	Finished product release testing, finished product stability testing	
Inspection readiness	Will be ready for inspection in mid-January, 2004	



ACCESS
PHARMACEUTICALS, INC.

N-000

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

December 4, 2003

RECEIVED
DEC 09 2003
RECEIVED
DEC 12 2003
CDR/CDER
MEGA/CDER

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12,229 Wilkins Avenue
Rockville, MD 20852

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. Original Submission

Dear Sir or Madam:

In accordance with 21 CFR 314.50, enclosed is an original 505(b)(2) New Drug Application for OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch). The required user fee payment was submitted on December x, 2003. A copy of the CTD Quality Information (Module 1, Module 2, and Module 3) is being sent concurrently to the FDA District Office in Dallas, TX. ✓

The facilities for the production of the drug product, [] will be available for inspection in late January, 2004 or any date thereafter. The facilities for the production of the drug substance, []

We appreciate the reviews and discussion by your staff during the IND stage of the development of the product. If you have any questions or additional comments, please contact me at (214) 905-5100 or at alc@accesspharma.com.

Sincerely yours,

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-727

APPLICANT INFORMATION

NAME OF APPLICANT Access Pharmaceuticals, Inc.	DATE OF SUBMISSION 12/4/03
TELEPHONE NO. (Include Area Code) (214) 905-5100	FACSIMILE (FAX) Number (Include Area Code) (214) 905-5101
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE RECEIVED DEC 09 2003 RECEIVED DEC 12 2003 CDR/CDER

PRODUCT DESCRIPTION

MEGA/CDER

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-727		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amlexanox 2mg, Mucoadhesive Patch	PROPRIETARY NAME (trade name) IF ANY OraDiscTMA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Amlexanox	CODE NAME (If any)	
DOSAGE FORM: Mucoadhesive Patch	STRENGTHS: 2 mg	ROUTE OF ADMINISTRATION: topical
(PROPOSED) INDICATION(S) FOR USE: treatment of Aphthous Ulcers		

PRODUCT DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION new dosage form for the treatment of aphthous ulcers
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>43</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. See attached List

ORIGINAL

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc

DMF #
DMF #
DMF #

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input checked="" type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input checked="" type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

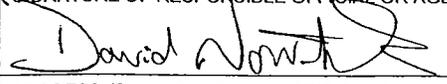
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE David P. Nowotnik, Ph.D.; Senior VP Research & Development	DATE: 12/4/03
ADDRESS (Street, City, State, and ZIP Code) 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	Telephone Number (214) 905-5100	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CBER, HFM-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway Suite 176 Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Will be ready for inspection in mid-January, 2004

MEMORANDUM OF TELECON

DATE: November 7, 2003, 2:00 PM

APPLICATION NUMBER: IND 59,949

DRUG PRODUCT: Amlexanox OraDisc

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development
Ric Zarzycki, Ph.D., Director, Quality Control and Logistics
Amy L. Campbell, Manager, Regulatory Affairs

Phone: 214-905-5100

Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Mary Jean Kozma-Fornaro, Chief, Project Management Staff
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: IND 59,949

The teleconference was requested by the Agency to discuss IND 59,949, Amlexanox OraDisc, in regard to the October 20, 2003 submission stating the Sponsor's opinion of having met the criteria required for a submission based upon a single pivotal study. In the August 13, 2003, the Agency felt that the requirement of very persuasive statistical findings for a single study did not appear to have been met. In the October 20, 2003 submission, the Sponsor provided several options, the Early and Final formulations, line extension and filing as a 505(b)(2) and wanted the Agency's advice on these options.

The Sponsor felt that the October 20, 2003 submission would save time and get feedback on a viable option.

The Agency expressed that it is the Sponsor's responsibility to decide on an option.

The Sponsor noted the Agency's position on the option decision being their responsibility.

The conversation ended amicably.

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

/s/

Mary Jean Kozma Fornaro
12/9/03 10:09:33 AM

MEMORANDUM OF MEETING MINUTES



Meeting Date: August 13, 2003 **Time:** 1:00 PM

Location: N225

Application: IND 59, 949, Amlexanox OraDisc
Guidance Meeting

Meeting ID: 11016

Sponsor: Access Pharmaceuticals, Inc.

Meeting Chair: Jonathan Wilkin, M.D., Director, DDDDP, HFD-540

Meeting Recorder: Jacquelyn Smith, Project Manager, DDDDP, HFD-540

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
John V. Kelsey, DDS, M.B.A, Dental Team Leader, DDDDP, HFD-540
Frederick Hyman, DDS, M.P.H., Dental Officer, DDDDP, HFD-540
Norman See, Ph.D., Pharmacology Reviewer, DDDDP, HFD-540
Chandra Chaurasia, Pharm.D., Pharmacokinetics, DPEIII, HFD-880
Mohamed Al-Osh, Ph.D., Team Leader, Biostatistics, DBIII, HFD-725
Steven Thomson, Ph.D., Biostatistician, DBIII, HFD-725
Wilson DeCamp, Ph.D., Team Leader, Chemistry, DNDCIII, HFD-830
Ernest Pappas, Chemistry Reviewer, DNDCIII, HFD-830
Jonca Bull, M.D., Director, ODE V, HFD-105
Terri Rumble, R.N., B.S.N/Associate Director of Regulatory Affairs, ODE V, HFD-105
Brian Harvey, M.D., Deputy Director, ODE V, HFD-105
Leonthena Carrington, Project Manager, DDDDP, HFD-540
Virginia Giroux, Project Manager, DDDDP, HFD-540
Millie Wright, Project Manager, DDDDP, HFD-540
Jacquelyn Smith Project Manager, DDDDP, HFD-540

External Constituent Attendees and Titles:

David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development, Access Pharmaceuticals, Inc.
Christiane M. Baud, Ph.D., Vice President, Clinical Development, Access Pharmaceuticals, Inc.
Amy L. Campbell, Manager, Regulatory Affairs, Access Pharmaceuticals, Inc.
J, Biostatistics Consultant
J Medical Consultant (via teleconference)

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

This meeting package contained a list of specific questions regarding CMCs. However, it is noted that the Sponsor did not address all of the CMC issues conveyed to them during the EOP-2 meeting of 8/20/01 and in the meeting minutes of 11/02/01. Some of the CMC issues were mentioned in the proposed meeting package. It is also noted that the Sponsor's amendment of 4/5/03 contained some of the information as requested; however, they did not indicate if this information was in response of the meeting minutes of 11/02/01. The Sponsor should indicate if all of the CMC issues have been addressed and where to find this information. This should be done before the NDA is submitted.

The sponsor stated that they were aware that they may not have responded to all issues raised at the EOP2 meeting. Certain responses appeared in amendment N-014. They will submit a summary of responses to all the issues.

Sponsor's Question # 1

Access will summarize information from Aphthasol[®] (amlexanox oral paste) 5%, NDA# 20-511 for chemistry, manufacturing, and controls information on the amlexanox drug substance and reference the NDA for individual documents and supporting data. Only new information on the stability of the drug substance not included in the NDA 20-511 will be provided in the Amlexanox OraDisc[™] mucoadhesive patch submission. Does the Agency concur with this proposal?

Agency's Response:

The answer is yes, providing that the new stability information is also submitted to NDA holder of NDA 20-511.

In addition, even though "amlexanox mucoadhesive patch" was recommended during the EOP-2 meeting as a dosage form description, the Office of Drug Safety will have to approve this term, and may not approve it. This dosage form is not recognized in the CDER Data Standards Manual. We recommend that you consider an alternate such as [

]

Sponsor's Question # 2

Access proposes that the following tests are sufficient for the regulatory QC release of Amlexanox OraDisc[™] mucoadhesive patch:

- [
-
-
-
-

]

The test methods listed above will be provided in the briefing document. Are these methods acceptable to the agency, and meet the criteria for regulatory QC release testing?

Agency's Response:

As proposed in the meeting package, they appear to be acceptable. However, this does not rule out the possibility that additional information may be required following our review of the data. Therefore, this will be answered at the time of the NDA review.

Because of concerns that amlexanox [] the mucoadhesive layer, please consider expanding the appearance quality attribute to include a test for [] when the mucoadhesive layer is exposed. This should be included in both release and stability testing. FDA clarified that the previous request for [] (at the EOP2 meeting) had been reconsidered, and that dissolution would suffice for this purpose.

The sponsor stated that amlexanox was [] in the mucoadhesive layer, not dissolved. FDA acknowledged this, and noted that the appearance test was too subjective. A microscopic examination of the mucoadhesive layer [] may be needed.

Sponsor's Question # 3

Access will propose an expiry term of 12 months based on the stability data generated from three clinical batches. The stability data will be presented in the briefing package. Does the Agency concur with the proposed expiry term?

Agency's Response:

The data submitted in the briefing are sufficient (3 lots, 12 months at room temperature) to support an expiration date of 12 months. It is not clear if these lots are in the to-be-marketed package. Any additional data submitted with the NDA will be reviewed in support of your proposed expiry. Additional data may support a longer shelf life.

Pharmacology/Toxicology:

Sponsor's Question # 4

A complete set of nonclinical studies for oral administration of amlexanox formulated as tablets and as a paste has been completed and was included in the Aphthasol NDA # 20-5-11. Access will format the pharmacology, pharmacokinetics, and toxicology summaries (written and tabulated) from NDA 20-511 including any new information, but will not include study reports from NDA 20-511. However, any data/publications on other formulations not included in NDA 20-511 will be included in their entirety in the Amlexanox OraDisc™ mucoadhesive patch submission. Does the Agency find this acceptable?

Agency's Response:

Yes.

Biopharmaceutics:

Sponsor's Question # 5

Access would like to request a waiver of the requirement for the submission of evidence *in vivo* bioavailability according to 21 CFR 320.22. The drug product is a topically applied preparation intended for local therapeutic effect, an exemption allowed by 21 CFR 320.22(b)(2). Does the Agency concur?

Agency's Response:

No, the Agency does not concur. 21 CFR 320.22 (b)(2) reads as follows:

- b. For certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained *in vivo* measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug

product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

- (1) N.A.
- (2) The drug product:
 - (i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and
 - (ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

As your product is not administered by inhalation, it does not qualify under this section of the waiver provisions.

Sponsor's Question # 6

Access has conducted a single-dose pharmacokinetic study in which 18 subjects received one, two or three Amlexanox OraDisc™ mucoadhesive patches, and as part of the Phase 3 study, has determined the serum levels of amlexanox pre-dose and 2 hr post-dose on Day 4 of multiple dosing with Amlexanox OraDisc mucoadhesive patches in 31 patients. A summary of the results will be in the briefing package. Access will submit the (1) pharmacokinetic study and (2) the data from the Phase 3 study as the complete pharmacokinetic data package to support the NDA submission? Does the Agency find this acceptable?

Agency's Response:

The Agency recommends that each multiple dose study should include enough subjects to obtain a meaningful pharmacokinetic profile of the drug in question. It is noted that the Agency had made the following comments in its response dated March 28, 2002 to the Protocol review (IND 59,949, submission date: Dec. 26, 2001):

"The sponsor needs to clarify how they want to extrapolate data from a single dose study to multiple dose situation."

Also, pharmacokinetic profile under maximal use conditions in accordance to the proposed labeling is requested.

Sponsor's Question # 7

Access plans to include four clinical studies conducted with the Early formulation OraDisc product. In one of the studies the serum level of amlexanox pre-dose and 1 hr post-dose on Day 4 of multiple dosing with the first generation OraDisc product was measured in 55 patients. These data have been previously submitted to the IND, and a summary of the results will be included in the briefing package. Access will submit these results as supportive pharmacokinetic data for the current Amlexanox OraDisc™ mucoadhesive patch pharmacokinetic data package. Does the Agency find this acceptable?

Agency's Response:

Yes. However, it is noted that these studies will provide only indirect supportive data, and may not

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Additional Biopharmaceutics Comment:

We note that no studies have been conducted to assess the impact of food on the bioavailability/retention of the amlexanox OraDisc. In lieu of such information the Sponsor should recommend that the product be applied ζ } to ensure adhesion and proper drug release.

Clinical and Biostatistics:

Sponsor's Question # 8

Access has conducted a Phase 3 clinical trial including 701 patients with minor aphthous ulcers. The study report has been completed and will be submitted to the IND. A summary of the results will be provided in the briefing document. Access considers this study to be of sufficient quality to qualify as a single "very persuasive study" (from minutes of August 20, 2001 End-of-Phase 2 Meeting) in support of the submission. Does the Agency concur with this opinion?

Agency's Response:

The acceptability of the study to support drug approval would be a review issue. However, based on the analysis that you provide in the submission, your results do not appear to be "very persuasive." Based on that assessment, the Agency has reclassified this as a Guidance Meeting.

At this point, you could ζ

J1.

Another option would be to compare the OraDisc to the marketed formulation of Amlexanox (Aphthasol) – this would be a line extension. Whatever you decide to do, you are encouraged to come in for a meeting to get agreement with the Agency prior to conducting the study.

Discussion at the Meeting: The Sponsor expressed surprise that the Division did not consider the results of the completed study of the final formulation "very persuasive." They noted that they had accepted the Division's suggestion that they enroll patients with multiple aphthae in their study. They also noted that the Guidance Document, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," does not specify what level of statistical significance is considered very persuasive. The Division responded that even though the guidance doesn't specify a level of significance, it can be assumed that it would be a higher magnitude than that for statistical significance in a study that is to be one of two. In addition, the acceptability of the p-value would be impacted by other factors like the magnitude of the treatment effect. The statistical consultant for the Sponsor asked why the Division had not pointed out that the proposed study was not powered to achieve "very persuasive" statistical significance. The Division responded that the Sponsor had not said that this was to be a single-study submission and had not asked whether the study was powered for that situation. (Addendum: Following this meeting a review of the record was conducted. The Division is unable to find a statement by the Sponsor in the request for Special Protocol Assessment in which they say that they intend to seek approval based on a single study.)

A second line of discussion concerned whether there was a need for another study to support efficacy, since the "Early formulation" of the disc was similar to the to-be-marketed product and because another formulation of amlexanox is already marketed. The Sponsor argued that studies conducted with these other formulations should provide the necessary supportive evidence. The Division responded that even seemingly minor changes in formulation may affect the efficacy of a product, and studies in other formulations could not be considered pivotal.

Addendum (Response to the sponsor fax dated August 18, 2003):

The Sponsor, in their submission of August 18, 2003, reiterated their view that the results of the statistical analyses for Study AP-C-1U106 constitute very persuasive statistical findings, one of the requirements for a single study submission. In response, it should be noted that according to the study protocol, efficacy evaluation would start by testing the hypothesis that no overall treatment effect among the three treatment arms (amlexanox, vehicle and no treatment) using the Cochran-Mantel-Haenszel (CMH) test, and if this is significant then the amlexanox versus vehicle comparison would be tested using the CMH test as the primary analysis and using the logistic regression as a secondary analysis.

The sponsor's summary of the efficacy results of Study AP-C-1U106 shows that the p-value for the overall test for the percentage of subjects with all treated ulcers healed at Day 5 is 0.031 and the p-value for the primary analysis for testing amlexanox versus vehicle is 0.015. It should be noted that the highly significant p-value for testing amlexanox versus vehicle (p-value = 0.007) was based on fitting the logistic regression model. It is impossible to make judgements about the reported p-value without checking the fitted model, however, we note that logistic regression is specified as a secondary analysis in the protocol.

The Agency continues to feel that the requirement of very persuasive statistical findings for a single study submission do not appear to have been met. In addition to a very small p-value, the magnitude of treatment effect compared to the vehicle, and internal consistency of efficacy results across study and subgroups also impact on the persuasiveness of the study. The sponsor is again referred to the Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

Sponsor's Question # 9

Access plans to include four clinical studies conducted with the Early formulation OraDisc product. Data for these studies have been previously submitted to the IND, and a summary of the results will be provided in the briefing package. These studies will be pooled in a comprehensive database used to evaluate clinical safety in patients. Does the Agency agree that data from the Early formulation OraDisc product can be added to the safety database?

Agency's Response:

If you were to submit the NDA at this time, the Agency would like to have the safety data on the Early formulation submitted in the NDA, but it should be separate from the safety data on the Final formulation.

Sponsor's Question # 10

Access plans to include four clinical studies conducted with the Early formulation OraDisc. A summary of the results will be provided in the briefing package. These studies will be included as supportive data for the efficacy of the Final formulation. Does the Agency agree that these data can be used as supportive data for efficacy of the current Amlexanox OraDisc™ mucoadhesive patch?

Agency's Response:

If you were to submit the NDA at this time, the utility of the data on the Early formulation would be a review issue.

Sponsor's Question # 11

Access has conducted clinical studies that included a total of 128 pediatric patients (67 on active) and compiled a pediatric database. A summary of the safety results will be provided in the briefing package. Access considers the data to be of sufficient quality to support a pediatric indication. Does the Agency concur?

Agency's Response:

The utility of the pediatric data to support a pediatric indication would be a review issue.

Sponsor's Question # 12

Access plans to submit the Amlexanox OraDisc NDA in the paper CTD format. Does the Agency find this acceptable?

Agency's Response:

Yes. The Agency's contact person for CTD submissions is Gary Gensinger: (301) 827-7753.

Sponsor's Question # 13

In order to facilitate review of the NDA, Access will submit portions of the submission in electronic format in addition to the paper CTD. Access plans to prepare a folder system with documents saved in Adobe Acrobat format without hyperlinks. Our clinical safety and efficacy databases will be submitting in SAS datasets. Does the Agency find these formats acceptable for electronic submission?

Agency's Response:

Yes. The Agency would like to have a paper copy of the summary of the NDA (Vol.1) to facilitate supervision of the review. We would also request annotated case report forms indicating variable names and resident dataset for each variable. Algorithms for derived variables should also be included.

For additional information, please refer to the guidance, Providing Regulatory Submissions in Electronic Format-NDAs, <http://www.fda.gov/cder/guidance/2353fnl.pdf>. The contact person is Gary Gensinger: (301) 827-7753.

Sponsor's Question # 14

Access plans to place the clinical studies conducted with the first-generation OraDisc product in Module 5, Section 5.3.5.4 (Efficacy and Safety Studies) Other Study Reports. Does the Agency agree that this section is the appropriate place for these data?

Agency's Response:

If you were to submit the NDA at this time, this is an acceptable place to report the data from the studies using the Early formulation, but the utility of the data from these studies remains a review issue.

Project Management:

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

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Jacquelyn Smith
9/12/03 01:26:24 PM
CSO

Chemistry, Manufacturing and Controls:

Sponsor's Question # 1: The Sponsor will modify the formulation of OraDisc™ . Details of the formulation are provided in the Chemistry Manufacturing and Controls Section of this document. The Sponsor proposes that the old and new formulations are sufficiently similar to allow for use of data from our recently completed Phase 2/3 clinical study in the NDA. The Sponsor wishes to know whether the Agency concurs with this proposal?

FDA Response: The answer is no, these formulations are not similar. The new excipients in the backing give added assurance of the rate of erosion of the wafer in the mouths. However, the mucoadhesive layer is significantly different, especially with regard to the concentration of amlexanox, [] in the new formulation, although the amount per patch remains the same.

The chemist has the following requests:

1. The excipient, [] is a trade name designation and should be identified by its chemical name. If it is a novel excipient, never used in a US approved product, a DMF or equivalent information, should be provided to the IND.
2. Under item B. (pg. 19)- Name and Address of Manufacturer for backing layer, please indicate if more than one manufacturing site is used.

Sponsor's Question # 2: A dissolution test method and preliminary test results for Amlexanox OraDisc™ are provided in the CMC Section of this document. The Sponsor wishes to know whether this method is acceptable to the agency, and meets the criteria described by the Agency at the pre-IND meeting on November 10, 1999.

FDA Response: The answer is yes. However, the [] speed [] seems high - is this an error?

[]

Sponsor's Question # 3: A [] test method for Amlexanox OraDisc™ is provided in the CMC Section of this document. The Sponsor will compare the old OraDisc™ formulation with the new formulation. The Sponsor does not plan to conduct any other types of *in vitro* tests. Does the Agency concur?

FDA Response: [] however; this drug product does not meet that criterion.

Sponsor's Question # 4: The Sponsor proposes the [] for the dosage form. Does the Agency concur?

FDA Response: The answer is no. We refer you to the CDER Data Standards Manual. It should be described as "amlexanox mucoadhesive patch." Please address in labeling accordingly.

Additional Comments:

1. The stability statement on page 24 of the meeting package is ambiguous in that it does not include a stability protocol. Please clarify.

During our pre-IND meeting on November 11, 1999, we recommended that, during the Phase 3 studies, stability data should be obtained on three (3) batches, using an acceptable stability protocol, which should be promptly submitted to the IND. The primary batches should be of the same formulation and packaged in the same container/closure system as proposed for marketing to simulate production batch. Two of the three batches should be at least pilot scale batches and the third one can be a smaller scale production batch, provided that the manufacturing process meaningfully simulates that which would be used for large scale batches for marketing. Reduced requirements for the submission of stability data are described in ICH Q1c "Stability Testing for New Dosage Forms," available on our Internet site. We recommend that you consult this and related guidances to determine the appropriate length of your stability studies for your planned NDA submission.

2. []
3. Where appropriate, [] should be described in the bulk as an in-process control during the manufacture of the amlexanox film.
4. We recommend that you assure yourselves that all manufacturing sites for Amlexanox OraDisc are ready for inspection at the time of the NDA submission.

Pharmacology/Toxicology:

Sponsor's Question #5 A complete set of toxicological studies for oral administration of amlexanox...is included in NDA 20-511. In addition, amlexanox has been tested in a mouse lymphoma assay. The sponsor believes that the non-clinical database is sufficient to support an NDA for Amlexanox OraDisc, 2mg, without the generation of additional toxicological data. Does the agency concur?"

FDA Response: The database appears to be adequate to support filing of a NDA with respect to the safety of amlexanox. Please note that the NDA should contain appropriate data to support the proposed exposure to each excipient in the product, as well as any impurities that may be present. In particular, it is unclear if the excipients [] are adequately qualified. They are present in the new formulation [] and the product would be orally administered to healthy individuals on a chronic basis. Unless the sponsor can document that a given excipient is qualified under the proposed conditions of exposure (e.g., GRAS as a direct food additive, present in a drug product that is approved for chronic oral administration to essentially healthy individuals, etc.), then data needed to support the proposed exposure to that excipient may include chronic toxicology data, reproductive toxicology data, genetic toxicology data, and carcinogenicity data. It is recommended that the sponsor submit an amendment to the IND in the near future that discusses each excipient and explains why the sponsor believes it is (or will be) qualified within the context of an NDA.

The NDA should explain why the drug product or backing material would not be aspirated (including while a patient was asleep), and why the potential to induce choking is not an issue.

Biopharmaceutics:

We concur with the reviewing FDA chemist in that use of [] test is not warranted by the data supplied by the sponsor in this package. As for their in vitro dissolution, the method as proposed uses a [] We feel this is an excessive speed and would

like to see dissolution results using more traditional speeds as outlined in the USP and in FDA guidance documents.

From discussions with the sponsor during the meeting it was learned that the recently conducted phase 2/3 trial did in fact use the old formulation. As the Agency considers the old and new formulations to be different, a new in vivo trial will be required. As to the related issue of bridging of the clinical data, evaluation of the erratic nature of amlexanox plasma levels suggest that in vivo biotesting is not likely to be successful in establishing bioequivalence. In lieu of pk linkage the sponsor was advised to consider an in vivo clinical trial to establish the equivalence of these two formulations.

Clinical:

Sponsor's Question #7: The Sponsor has conducted a Phase 2/3 clinical trial including 401 patients with minor aphthous ulcers using the old formulation. The study report has been completed and submitted to the IND. A summary of the results is provided in the Clinical Report Summary section of this document. The Sponsor considers this study to be of sufficient quality to qualify as one of the pivotal studies. Does the Agency concur?

FDA Response: The Agency does not consider the two formulations of OraDisc™ to be sufficiently similar to allow the data from the completed study to be used as pivotal for approval of the new formulation. The Sponsor [In addition, the Division makes commitments regarding study design at the End-of-Phase 2 meeting. Because you declined to have an EOP2 meeting, you don't have benefit of commitments regarding the completed study. The utility of the completed study in supporting an NDA submission will be a review issue. Given the information available about other formulations of amlexanox, the Agency might be willing to accept a single study to support filing of an NDA, but it would have to be a very persuasive study, with robust results and no significant flaws. The Sponsor is referred to FDA's "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," for discussion of the issue.

Sponsor's Question #8: The Sponsor proposes to conduct a pivotal trial of amlexanox OraDisc™ (new formulation) versus vehicle disc and no treatment. The design and statistical analyses will be identical to those of the recently completed Phase 2/3 trial. An outline of the proposed pivotal trial and statistical hypothesis is provided in this document. Does the Agency concur? (The Sponsor submitted the complete protocol as Serial 011.)

FDA Response: The Division has the following comments about the proposed Phase 3 study:

1. The inclusion of pediatric patients only down to age 12 seems reasonable, given the potential difficulty of applying and maintaining the dosage form in the mouth, but the lower end of the age range should be significantly represented.
2. The Sponsor does not state whether adverse event information will be solicited from the patient, or simply reported if the patient spontaneously provides the information. There should be a system for actively soliciting such reports, perhaps including a script. A question regarding aspiration or other problems with the dosage form should be included.
3. The Division has concerns about the fate of the backing material. The Sponsor states that it can be swallowed, but is it resorbable? It would seem that there is some risk of aspiration, particularly if the patient goes to sleep with the disc in place. The Sponsor should have a plan to document the fate of the backing material and should discuss the associated safety issues.

4. The Sponsor proposes to have patients treat a single ulcer, even if there are multiple ulcers present. In actual use, patients who have multiple ulcers would likely use more than one OraDisc™ at a time. The Division would prefer a trial design that permits evaluation of the safety and efficacy of the product under conditions of actual use.
5. The criteria for success were not clear from the submission. The criteria that the Division is willing to commit in advance to accept would be that in order to “win,” active will have to beat vehicle and vehicle will have to be non-inferior to no treatment.
6. The Sponsor is reminded that the ICH E1a guidance recommends that in the case of a chronic use drug, a minimum of 300-600 patients be on active for at least six months. Given the safety information available about amlexanox and the fact that aphthous ulcers is an acute, short term pathology, the Agency would be willing to defer long term safety studies to Phase 4. The Sponsor should clarify its plans for assessing long term safety.
7. The Sponsor should understand that the submitted protocol as modified by FDA comments constitutes the EOP2 commitments made by the Division. Subsequent protocol amendments must be submitted to the FDA, but FDA receipt of these protocol amendments does not constitute a commitment to consider that amendment acceptable in the NDA review. Generally the Division will only contact the Sponsor regarding a protocol amendment if that amendment raises a safety concern. If the Sponsor desires FDA commitment regarding a specific protocol amendment, they should submit the amendment(s) for FDA consideration as a 45-day Special Protocol Assessment request.

Biostatistics:

1. The primary efficacy endpoint should be defined as the proportion of patients with complete healing of all ulcers. Several secondary endpoints involving pain resolution and ulcer healing have been proposed.
 - (a) Note that although an analysis for time to healing has been proposed, it is not listed as a secondary endpoint.
 - (b) The secondary endpoints will be assessed at a large number of timepoints. An adjustment for multiplicity may be necessary if the results are to be used in labeling.
2. The protocol should clarify what must be demonstrated by the pairwise comparisons among the three treatments to establish efficacy. The active treatment should be superior to vehicle, and the vehicle should be non-inferior to no treatment. A non-inferiority margin should be specified in the protocol so that non-inferiority can be assessed.
3. The protocol states that both 95% and 97.5% confidence intervals will be used “as appropriate”. The protocol should clarify when it is appropriate to use the two levels. A test of hypothesis with $\alpha=0.05$ should be used to assess the superiority of active over vehicle, and a one-sided 97.5% confidence interval (with an appropriate non-inferiority margin) should be used to assess the non-inferiority of vehicle to no treatment.
4. The method for handling missing data in the ITT population should be provided.
5. In the analysis of the primary efficacy endpoint, the Cochran-Mantel-Haenszel test should be the primary analysis, with the logistic regression being secondary. The protocol should be clear about which analysis is primary.

6. The sponsor is encouraged to use a limited number of covariates in the logistic regression and log-rank models. For a confirmatory trial, only a small number of covariates should be specified in the protocol, and all of the specified covariates should be retained in the final model. This method is preferred over testing all possible covariates for significance in confirmatory trials.
7. The protocol should include a method of assessing treatment by center interaction in the primary analysis.
8. The Division recommends enrolling at least 10 subjects per treatment arm per center to avoid problems with small centers in the analysis. However, the protocol should also specify a plan for combining centers (based on the number of patients, or geographic region) in case the enrollment targets are not met.

All comments are based upon the briefing document, which is an unofficial document submitted as information. The final protocols should be submitted to the IND for review.

Pediatric Studies:

The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following: Per 21 CFR 314.50(d)(7), NDA applications are required to *contain a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, and information required to be submitted under Section 314.55.*

In addition, per 21 CFR 314.55(a), each NDA application for a new ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Under 21 CFR 314.55(d) this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter. A waiver can be requested in accordance with 21 CFR 314.55(c).

Financial Disclosure:

The Final Rule regarding Financial Disclosure was published on February 2, 1998, for applications submitted after February 2, 1999, the applicant is required either to certify the absence of certain financial interests and arrangements of clinical investigators or to disclose those financial interests.

Minutes Preparer: _____
Victoria Lutwak/Project Manager, DDDDP

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP

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/s/

Jonathan Wilkin

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