

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-727**

**Chemistry Review(s)**

**NDA 21-727**

**Tradename  
(2mg Amlexanox, Mucoadhesive Patch)**

**Access Pharmaceuticals, Inc.**

**Ernest G. Pappas**

**Division of Dermatological and Dental Drug Products**

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On Original



# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

### Chemistry Review Data Sheet

1. NDA 21-727
2. REVIEW #: 1
3. REVIEW DATE: 9/20/04
4. REVIEWER: Ernest G. Pappas
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original	12/4/03
Amendment	2/27/04
Amendment	3/15/04
Amendment	8/30/04
Amendment	9/20/04

Note: Amendment dated 3/15/04 indicated that FDA's request of 2/0/04 regarding questions raised via Filing Review Letter was answered with the 3/15/04 amendment (see below).

7. NAME & ADDRESS OF APPLICANT:

Name: Access Pharmaceuticals, Inc.  
Address: 2600 Stemmons Freeway, Suite 176  
Dallas, TX 75207-2107  
Representative: David P. Nowotnik, Ph.D;  
Senior VP Research

# CHEMISTRY REVIEW TEMPLATE

## Chemistry Assessment Section

Telephone: (214) 905-5100

8. DRUG PRODUCT NAME/CODE/TYPE: Amlexanox; AA-673
- a) Proprietary Name: OraDisc™ A
  - b) Non-Proprietary Name (USAN): Amlexanox 2 mg, Mucoadhesive Patch
  - c) Code Name/# (ONDC only)
  - d) Chem. Type/Submission Priority (ONDC only):
    - Chem. Type: 3
    - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)
10. PHARMACOL. CATEGORY: Treatment of Aphthous Ulcers
11. DOSAGE FORM: Mucoadhesive Patch
12. STRENGTH/POTENCY: 2 mg
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

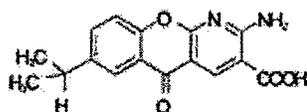


# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT: 298.30



Amlexanox

17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	IV	[ ]	[ ]	7	Never reviewed	Not required	USP monograph.
2	IV	[ ]	[ ]	7	Never reviewed	Not required	USP monograph
3	III	[ ]	[ ]	3	Acceptable		Reviewed 4/12/02

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
n/a		

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES			
LNC (DMETS)	Tradename( <i>OraDisc™ A</i> ) not acceptable; all other acceptable.	7/19/04	Kristina Arnwine
Methods Validation	Not acceptable; MV package inadequate.	As of 8/27/04	
Microbiology	Acceptable	9/17/04	Bryan Riley

19. ORDER OF REVIEW (OGD Only)    NA

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No    If no, explain reason(s) below:

**The Chemistry Review for NDA 21-727**

**The Executive Summary**

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

This NDA can be approved from a Chemistry standpoint. However, there are some minor CMC and labeling issues that need resolution by the applicant.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

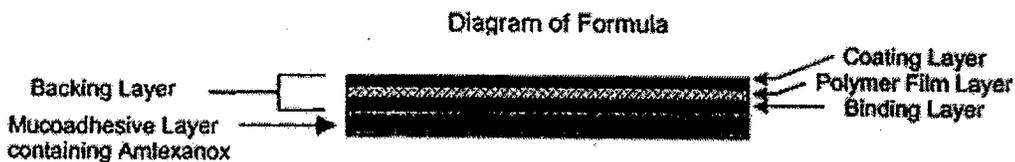
None

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

Amlexanox 2 mg, Mucoadhesive Patch, packaged in units of 20 patches in a sealed HDPE bottle, with a [ ] cap with foil seal.

This patch is made up of four layers; a mucoadhesive layer that is to come in contact with the mucosal tissue the, a binding layer, a polymer film layer, and a coating layer. This film has the following configuration:



The drug substance is the same API that was approved for Aphthasol®, Amlexanox Oral Paste 5% (NDA 20-511) for the treatment of aphthous ulcers in the mouth.

There are [ ] that were observed in the manufacture of Amlexanox 2 mg, Mucoadhesive Patch. They are as follows:

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## Chemistry Assessment Section

In this regard, in-process controls are performed to assure

In addition, the release specifications give added assurance of the identity, strength, quality and purity for the finished product.

The applicant proposed a tentative expiration date of 12 month when stored at 25 °C (Control Room Temperature). Acceptable stability data were submitted to support ambient storage conditions (25 ± 2 °C/ 60% RH). However, the stability data failed dissolution testing at accelerated and intermediate conditions and respectively. The firm indicated that, after evaluating the properties of Amlexanox at temperatures above 25 °C. A 12 month expiration date has been granted for the drug product.

The tradename, OraDisc™ has been found not acceptable by DMETS. This reviewer agrees with DMETS because of the "Look-Alike/Sound-Alike Issues" to the marketed product "Orudis KT". Also, the label should reflect a storage statement of 25°C with a Caution statement "Do Not Store above 30°C".

**Establishment Inspection:** An overall recommendation of "Approvable" were given for the four facilities from the Office of Compliance as of 9/14/04 (see pg. 77 below).

**Environmental Assessment:** The applicant claims a categorical exclusion from the preparation of an Environmental Assessment for OraDisc™ A, Amlexanox 2 mg, Mucoadhesive Patch as described in 21 CFR 25.31 (c). The firm provided the calculations to show EIC level well below 1 ppb. as per 21 CFR 25.31 (b).

### B. Description of How the Drug Product is Intended to be Used

#### ROUTE OF ADMIN.: Topical

The OraDisc is placed on the mucosal tissue of mouth. The mucoadhesive polymers ensure the adhesion to mucosal tissue. The mucoadhesive layer swells upon contact with the saliva. While the backing layer is progressively dissolving and eroding into the saliva, the drug is being delivered at

## CHEMISTRY REVIEW TEMPLATE

### Chemistry Assessment Section

the site of application. After subsequent erosion, the remaining pieces of the patch are dislodged and swallowed.

#### **C. Basis for Approvability or Not-Approval Recommendation**

The manufacturing and controls as identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug product. However, there are some minor CMC and labeling issues that need resolution by the applicant.

### **III. Administrative**

#### **A. Reviewer's Signature:**

#### **B. Endorsement Block**

Chemist Name/Date: Ernest G. Pappas/9/24/04  
ChemistryTeamLeaderName/Date: Norman R. Schmuff /  
ProjectManagerName/Date/ Jacquelyn Smith/

#### **C. CC Block:**

**HFD-540/Division File**  
**HFD-540/Pappas**  
**HFD-540/Hyman**  
**HFD-540/Lee**  
**HFD-540/See**  
**HFD-540/Chaurasia**

82 Page(s) Withheld



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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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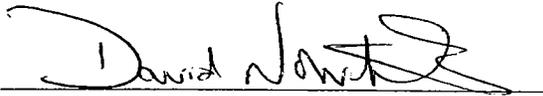
Ernest G. Pappas  
9/24/04 10:20:29 AM  
CHEMIST

My chemistry review has been completed. This review contains  
the corrections to the IR Deficiencies observed. Recommend  
approval of the NDA from a CMC standpoint.

Norman Schmuff  
9/24/04 11:16:03 AM  
CHEMIST

### 1.3.6 Environment Assessment Waiver

Access Pharmaceuticals, Inc., hereby claims a categorical exclusion from the preparation of an Environmental Assessment for OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch as described in 21 CFR 25.31(c).



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