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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-594

Medical Review(s)



Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5365, FAX (301) 594-5494

Memorandum

DATE: 2.03.04
FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
SUBJECT: NDA 21-594
NAME OF DRUG: Amiodarone hydrochloride injection
SPONSOR: International Medication Systems, Ltd., (IMS)

DOCUMENTS USED FOR MEMO:

1. Prior approvable memo for 21-594
2. Project Manager's overview, by Russell Fortney, dated 1.6.04.
3. Approved amiodarone labeling.
4. Patent information, section 13 of sponsor's NDA, dated 10.31.02.
5. Debarment certification, dated 10.31.02.
6. Biopharmaceutics review by B. Nhi Nguyen, Pharm. D., dated 4.18.03.
7. Chemistry reviews by J.V. Advani, Ph.D., dated 1.23.04 and 8.22.03.
8. Establishment Evaluation Report, dated 5.09.03.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum decision of an approval action for the NDA named above for amiodarone hydrochloride injection. All items identified in the Approvable letter have been resolved satisfactorily.

BACKGROUND AND OVERVIEW OF RESPONSE TO APPROVABLE ACTION

The first major issue outstanding at the time of the Approvable action was a 'withhold approval' recommendation for the cGMP status of the manufacturing facility in South El Monte CA. The Office of Compliance sent the following in this regard:

"Our concurrence with LOS-DO to withhold approval of this application is based on a recommendation made by HFD-326 that LOS-DO conduct a regulatory meeting with IMS during which CGMP deficiencies uncovered during a 4/22/03-5/9/03 inspection will be discussed. During that meeting, LOS-DO is to inform representatives of IMS that all pending applications in the SVS profile class will be withheld until confirmation of correction of the CGMP deficiencies."

The withhold recommendation has been lifted by the Office of Compliance, as of 12.05.03, although the precise responses made to the deficiencies identified in the Establishment Evaluation Report, dated 5.09.03, are not known to me or the review Chemist. I assume, but have no way of verifying at present, that a follow-up inspection took place.

The other major issue had to do with agreeing to labeling, especially the placement of the cartoon depicting the use of the product. The current placement has been agreed to by both the Agency and the sponsor.

SUMMARY

No new issues have been identified and the deficiencies noted in the Approvable action have been addressed. The application for amiodarone hydrochloride injectable can be approved under 505(b)(2).

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/s/

Doug Throckmorton
2/3/04 12:41:18 PM
MEDICAL OFFICER



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Memorandum

DATE: 9.05.03
FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
SUBJECT: NDA 21-594
NAME OF DRUG: Amiodarone hydrochloride injection
SPONSOR: International Medication Systems, Ltd., (IMS)

DOCUMENTS USED FOR MEMO:

1. Proposed labeling for product.

BACKGROUND AND CONCLUSIONS

This follow-up memo is an addendum to the Divisional approvable memo, and covers a specific area of labeling. The sponsor has proposed to place a cartoon of the container and its use in the How Supplied section of the labeling. Reviewing other labeling for approved drugs, I find such instructions for use typically are placed in the Dosage and Administration (D/A). In particular, Lovenox includes a picture such as the one proposed in this case, in the D/A section. In a broader context, how to mix and administer other intravenous cardiac products (Epogen, Dofetilide, Natricor) is included in the D/A, and not in the How Supplied. An assertion has been made that the Office of Generic Drugs routinely includes such information in the How Supplied section, but no rationale for that placement has been submitted, and the 'routine' nature of that practice is not known to me. The sponsor should move the picture into the D/A section (it does, after all, inform 'administration' of the drug).

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/s/

Doug Throckmorton
9/5/03 04:21:32 PM
MEDICAL OFFICER



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Memorandum

DATE: 10.16.02
FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110
SUBJECT: NDA 21-594
NAME OF DRUG: Amiodarone hydrochloride injection
SPONSOR: International Medication Systems, Ltd., (IMS)

DOCUMENTS USED FOR MEMO:

1. Chemistry Review #1 by J.V. Advani, Ph.D., dated 8.22.03.
2. Clinical Pharmacology and Biopharmaceutics Review by B. Nhi Nguyen, Pharm.D., dated 10.30.02.
3. Microbiology Review, by James L. McVey, Ph.D., dated 5.01.03.
4. Statement from Office of Compliance regarding inspections, from EES.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum decision of an approvable action for the NDA named above for amiodarone hydrochloride injection. Items pending resolution include resolution of the issues leading to the 'withhold approval' recommendation from the Office of Compliance.

BACKGROUND AND OVERVIEW OF REVIEWER'S FINDINGS

This application is a 505 (b)(2), relying on the findings of safety and efficacy data from the approved Cordarone IV product. In particular, the application consists of a container change only (change to a Dilute-A-Jet Additive syringe system). In retrospect, this should almost certainly have been an application submitted to the Office of Generic Drugs and not to the DCRDP. The necessary waiver for any need to assess bioavailability was given by the Clinical Pharmacology review, and no other issues were identified by her in her review (which includes a recommendation for approvability of the application). The Microbiology reviewer recommended approval from a product quality microbiology perspective. The only issue identified by the Chemistry reviewer was a resolution of the 'withhold approval' recommendation for the cGMP status of the manufacturing facility in South El Monte CA. The Office of Compliance sent the following in this regard:

"Our concurrence with LOS-DO to withhold approval of this application is based on a recommendation made by HFD-326 that LOS-DO conduct a regulatory meeting with IMS during which CGMP deficiencies uncovered during a 4/22/03-5/9/03 inspection will be discussed. During that meeting, LOS-DO is to inform representatives of IMS that all pending applications in the SVS profile class will be withheld until confirmation of correction of the CGMP deficiencies."

SUMMARY

The application for amiodarone hydrochloride injectable is approvable pending resolution of the cGMP issues. A letter with that as the listed deficiency should be drafted.

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/s/

Doug Throckmorton
9/3/03 10:07:42 AM
MEDICAL OFFICER

International Medication Systems, Limited

Section 9

New Drug Application, NDA
Product: Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL

Section 9 Safety Update Report

Safety Update Report



International Medication Systems,
Limited

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South El Monte, CA 91733

International Medication Systems, Limited

Section 9

New Drug Application, NDA
Product: Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL (Prefilled Syringe)

Section 9 Safety Update Report

There is no Safety Update Report information included in this Application. In accordance with 21 CFR 314.54(a)(vii)(3), International Medication Systems, Limited has relied on the listed reference drug, Wyest-Ayerst's Cordarone® Intravenous Injection (NDA 20-377).

**APPEARS THIS WAY
ON ORIGINAL**

International Medication Systems, Limited

Section 10

New Drug Application, NDA
Product: Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL

Section 10 Statistical Section

Statistical Section



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International Medication Systems, Limited

Section 10

New Drug Application, NDA
Product: Amiodarone Hydrochloride Injection
50 mg/mL, 3 mL and 18 mL (Prefilled Syringe)

Section 10 Statistical Section

There are no description of statistical evaluations included in this Application. These description is not required since not clinical studies were performed by International Medication Systems, Limited to support this application. International Medication Systems, Limited has relied on the listed reference drug, Wyest-Ayerst's Cordarone® Intravenous Injection (NDA 20-377).

**APPEARS THIS WAY
ON ORIGINAL.**