CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-594

Administrative/Correspondence

Section 13 Patent Information On Any Patent Which Claims The Drug

Patent Information On Any Patent Which Claims The Drug

International Medication Systems, Limited
1886 Santa Anita Ave.
South El Monte, CA 91733

Section 13 Patent Information On Any Patent Which Claims The Drug

A patent search was performed to locate any drug substance, drug product or method of use patents regarding Amiodarone HCl Injection.

International Medication Systems, Limited intended to certify that in our opinion and to the best of our knowledge, there are no patents, active or valid, that claim the proposed drug in this Application, Amiodarone HCl Injection (prefilled syringe).

Section 14 Patent Certification

Patent Certification with Respect to Any Patent Which Claims The Drug

International Medication Systems, Limited
1886 Santa Anita Ave.
South El Monte, CA 91733

Section 14 Patent Certifiation

Reference is made to the *Approved Drug Products with Therapeutics Equivalence Evaluations, 20th Edition.* Amiodarone Hydrochloride Injection; Cordarone® (NDA 20-377) is listed in the ``Prescription and OTC Drug Product Patent and Exclusivity Data". Refer to the following pages for a copy.

Paragraph I Certification

In the opinion and to the best knowledge of International Medication Systems, Limited, there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

Exclusivity

According to the above mentioned published information, the reference listed drugs, Cordarone® is entitled to a period of orphan drug exclusivity, which will be expired on August 03, 2002, under Section 505(j)(4)(D) of the Food, Drug and Cosmetic Act.

Stephen A. Campbell
Vice President, Regulatory Affairs
International Medication Systems, Limited

10/31/02
Date

EXCLUSIVITY SUMMARY for NDA # 21-594 SUPPL # _____

Trade Name N/A Generic Name Amiodarone

Applicant Name International Medication Systems, Ltd. HFD-110

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   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 /___/ NO /X_/

      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.

      This is a 505(b)(2) application. No clinical trial data was submitted.

      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 /___/ NO /_X_/

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

_____

_____

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/ NO /___/

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

NDA # _____ _____

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.)

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /___/ 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 9:**

_____

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title: _____

_____ _____

Signature of Office or Division Director Date

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

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA # : 21-594 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 11/8/02 Action Date: _____

HFD-110 Trade and generic names/dosage form: Amiodarone hydrochloride injection

Applicant: Internationals Medication Systems, Ltd Therapeutic Class: Anti-arrhythmic

Indication(s) previously approved: N/A

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

Number of indications for this application(s): _____

Indication #1: Initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

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._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	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: _____

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.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ 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}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**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:**_____

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.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

Section 16 Debarment Certification

Debarment Certification

International Medication Systems, Limited
1886 Santa Anita Ave.
South El Monte, CA 91733

Section 16 Debarment Certification

Debarment Certification

International Medication Systems, Limited 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.

International Medication Systems, Limited further certifies that neither the applicant nor any affiliated persons responsible for the development or submission of this application have been convicted as described in subsection (a) and (b) [sections 306(a) and 306(b)] within the previous 5 years.

Stephen A. Campbell
Vice President, Regulatory Affairs
International Medication Systems, Limited

10/31/02
Date

RHPM NDA Overview
January 6, 2004

Application:	NDA 21-594
Drug Name:	Amiodarone Hydrochloride Injection 50 mg/ml (3 ml & 18 ml prefilled syringe)
Sponsor:	International Medication Systems, Ltd.
Classification:	5 S
Indication:	Initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.
Date of Application:	October 31, 2002
Date of Receipt:	November 8, 2002
Goal Date:	February 4, 2004

This NDA was submitted to the Division on November 8, 2002 as a 505(b)(2) application. The reference listed product is Cordarone IV®. The Sponsor's reason for submitting a 505(b)(2) application rather than a generic application was the product would be supplied in a pre-filled syringe (the reference listed product in supplied in ampules). A Refuse-To-File letter should have been issued directing the Sponsor to file as a generic [505(j)], as a change in packaging container such as with this product is not a valid basis for a 505(b)(2) filing. However, the application was filed in the Division as a 505(b)(2).

An approvable letter was issued on September 5, 2003. Because of manufacturing deficiencies, the Office of Compliance had recommended "withhold" approval. In addition, the Division asked that the syringe assembly directions be moved from the **HOW SUPPLIED** section to the **DOSAGE AND ADMINISTRATION** section of the labeling.

The Office of Compliance changed the status from "withhold" to "acceptable" on November 5, 2003. The sponsor submitted FPL on December 2, 2003, with the syringe assembly instructions appropriately moved, to satisfy all requirements of the September 5, 2003 approvable letter.

Biopharmaceutics:

Reviewer:	Nhi Nguyen, Pharm. D.
Labeling:	Labeling is similar to Cordarone's, except for differences in packaging.
Conclusion:	According to CFR 320.22(b)(1), the in vivo bioavailability of this product is self-evident and the sponsor does not have to prove in a human bioavailability study that their product is bioequivalent to Cordarone IV®. This application may be approved.

Chemistry:

Reviewer:	J.V. Advani, Ph.D.

Labeling:	Labeling is acceptable.
cGMP Inspections:	Current status is "Acceptable."
Methods Validation:	Methods validation packages for district laboratories have been provided.
Environmental Assessment:	Categorical Exclusion acceptable.
Conclusion:	This application may be approved.

Microbiology:

Reviewer:	James McVey, Ph.D.
Labeling:	Labeling is acceptable
Conclusion:	This application may be approved.

Medical:	Not needed.
Pharmacology:	Not needed.
Statistics:	Not needed.
DSI:	N/A (no clinical trial data submitted)
Postmarketing Commitments:	N/A
Exclusivity Checklist:	Included in package
Safety Update:	N/A
Pediatric Information:	N/A
Patent Information:	Included in package.
Debarment Certification:	Included in package.
Trade Name Review:	N/A
Advisory Committee Meeting:	No meeting held.
RHPM Comments:	All deficiencies noted in the approvable letter have been adequately addressed. An approval letter will be drafted for Dr. Throckmorton's signature.

/S/

Russell Fortney
RHPM
rf-1/6/03

31 pages redacted from this section of the approval package consisted of draft labeling

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-594**	Efficacy Supplement Type SE- **N/A**	Supplement Number **N/A**	
Drug: **Amiodarone Hydrochloride Injection**		Applicant: **International Medication Systems, Ltd.**	
RPM: **Russell Fortney**		**HFD-110**	Phone # **301-594-5311**
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): **Cordarone IV NDA-20-377**	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	**5S**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	September 8, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	**N/A**
• OC clearance for approval	**N/A**
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) (X) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	**X**

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	September 2, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE September 5, 2003**
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) 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)	
• Most recent applicant-proposed labeling	**X**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**N/A**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**X**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X**
• Reviews	**X**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**N/A**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**N/A**
❖ Memoranda and Telecons	**N/A**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**N/A**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**
❖ Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	**N/A**

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**N/A**
❖ Clinical review(s) *(indicate date for each review)*	**N/A**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Statistical review(s) *(indicate date for each review)*	**N/A**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**April 18, 2003**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**August 22, 2003, September 3, 2003, January 23, 2004**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**August 22, 2003**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**May 1, 2003**
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**N/A**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

International Medication Systems, Limited

1886 Santa Anita Ave.
South El Monte, CA 91733

2. TELEPHONE NUMBER *(Include Area Code)*

(626) 459 - 5253

3. PRODUCT NAME

Amiodarone HCl Injection, 50 mg/mL, 3mL and 18 mL (Prefilled Syringe)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, 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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice President, Regulatory Affairs	10/31/02

FORM FDA 3397 (4/01)

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application *or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted* below. Form 3397 should be placed in the first volume of the application with the application form.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval
Applications (including supplements) for:

- Products for further manufacturing only
- Whole Blood or Blood Component for Transfusion
- Bovine Blood Product for Topical Application Licensed before September 1, 1992
- A crude Allergenic Extract Product
- An *In-Vitro* diagnostic biological product licensed under section 351 of the PHS Act

ITEM NO.: **INSTRUCTIONS**

1-2. **Self-explanatory**

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **BLA STN / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the 6-digit Biologics License Application STN if known.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: N099999.

5. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Indusry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on CDER's web site: http://www.fda.gov/cder/pdufa/default.htm

6. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210. Questions regarding the CDER User Fee I.D. Number should be directed to CDER's User Fee Staff at (301) 594-2041.

FOR BIOLOGIC PRODUCTS - The User Fee I.D. Number is the applicant's four digit U.S. License Number, followed by a sequential number for each fee paying submission from the applicant; starting with number 1. If the firm is unlicensed, a number may be obtained by calling CBER's Regulatory Information Management Staff (RIMS) at (301) 827-3503. Questions regarding the CBER User Fee I.D. number should also be directed to RIMS.

EXAMPLE: For U.S. License Number 0222, the fifth submission would be given the User Fee I.D. Number: 0222-5.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); and NOT a new indication for a use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

The submission is a supplement for a new pediatric indication. Under section 736(a)(1)(F) of the FD&C Act, a supplement to a "human drug application" proposing to include a new indication for use in pediatric populations is not subject to a fee.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the submission.

MINUTES OF FILING MEETING

NDA 21-594
Amiodarone HCl injection 50 mg/ml, 3 ml and 18 ml
in the Dilute-A-Jet Additive Syringe delivery system

Applicant: International Medication Systems, Limited (IMS)

Date of Application: October 31, 2002
Date of Receipt: November 8, 2002
Goal Date: September 8, 2003

Filing Meeting Date: January 2, 2003

BACKGROUND:
IMS has submitted this NDA for amiodarone HCl injection as a 505(b)(2) application, as their product will be supplied in pre-filled glass syringes (Cordarone Intravenous, the reference listed drug, is supplied in glass ampules). The IMS product is identical to the referenced product in active ingredients, inactive ingredients and concentration. IMS will provide two different product sizes (3 ml and 18 ml), while Cordarone is available in only a 3 ml size.

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Division Director, HFD-110
Robert Shibuya Ph.D.	DSI
J.V. Advani, Ph.D.	Chemist, HFD-810
Nallaperum Chidambaram, Ph.D.	Acting Chemistry Team Leader, HFD-810
Patrick Marroum, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader, HFD-860
Albert DeFelice, Ph.D.	Pharmacology Team Leader, HFD-110
Zelda McDonald	Chief, Project Management Staff, HFD-110
Russell Fortney,	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	**Review Due Date**
Medical:	Norman Stockbridge, M.D., Ph.D.	N/A
Pharmacology:	Pritam Gill-Kumar, Ph.D.	N/A
Chemist:	J.V. Advani, Ph.D.	March 31, 2003
Biopharmaceutical:	Nhi Nguyen, Pharm.D.	N/A
Microbiology, sterility:	James McVey, Ph.D.	March 31, 2003
Project Manager:	Russell Fortney	

Per reviewers, all parts in English, or English translation? YES__X__ NO___

CLINICAL – File __X__ Refuse to file _____

- Clinical site inspection needed: YES_____ NO__X__

MICROBIOLOGY CLINICAL – File__X__ Refuse to file_____

STATISTICAL – File ___X___ Refuse to file _____

BIOPHARMACEUTICS – File ___X___ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X___

PHARMACOLOGY – File ___X___ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X__NO_____ File__X__ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

__X___The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

/S/

Russell Fortney
Regulatory Health Project Manager, HFD-110

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-594
Amiodarone HCl injection
50 mg/ml, 3 ml and 18 ml in the Dilute-A-Jet Additive Syringe delivery system

Applicant: International Medication Systems, Limited

Date of Application: October 31, 2002
Date of Receipt: November 8, 2002
Date of Filing Meeting: January 2, 2003
Filing Date: January 8, 2003

Indication(s) requested: Treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy

Type of Application: Full NDA __X__ Supplement _____
(b)(1) _____ (b)(2) __X__
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S__X__ P_____
Resubmission after a withdrawal or refuse to file __No__
Chemical Classification: (1,2,3 etc.) __5__
Other (orphan, OTC, etc.) __N/A__

Has orphan drug exclusivity been granted to another drug for the same indication? YES (now expired)

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: **N/A –505(b)(2)** Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__X__ NO_____
User Fee ID#_____
Clinical data? YES _____ NO __X__ Referenced to NDA# 20-377 (Cordarone Intravenous)
Date clock started after UN _____

User Fee Goal date: September 8, 2003

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
- **If foreign applicant, the U.S. Agent must countersign.**

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? N/A
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES

List referenced IND numbers: N/A

End-of-Phase 2 Meeting? N/A
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? N/A
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
N/A

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) package submitted? YES
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

-This application provides for a change in the container; IMS amiodarone will be supplied in pre-filled syringes.

Name of listed drug(s) and NDA #: Cordarone Intravenous, 50 mg/ml.

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

__X__ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-594

International Medication Systems, Limited
Attention: Mr. Stephen A. Campbell
Vice President, Regulatory Affairs
1886 Santa Anita Ave.
South El Monte, CA 91733

Dear Mr. 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: Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL and 18 mL (prefilled syringe)

Review Priority Classification: Standard (S)

Date of Application: October 31, 2002

Date of Receipt: November 8, 2002

Our Reference Number: NDA 21-594

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 January 7, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 8, 2003.

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:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
HFD-110
Attention: Document Room 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please contact:

Mr. Russell Fortney
Regulatory Health Project Manager
(301) 594-5311

Sincerely,

/S/

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research