

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-425

CHEMISTRY REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2009

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 22-425

SUBJECT: OC recommendation

RECOMMENDATION: The drug product MULTAQ (Dronedarone) film-coated tablet, 400 mg, is recommended as APPROVAL from a CMC perspective.

REVIEW NOTE:

The NDA 22-425 CMC review #1 was completed on 2/18/2008. All other CMC issues have been resolved, except one pending issue on the overall recommendation from the Office of Compliance (OC) on manufacturing facilities. We have now received the OC recommendation indicating no inspection concerns (issued on 4/27/09 - an overall recommendation of acceptable). The Establishment Evaluation Report summary is shown below.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22425/000 Sponsor: SANOFI AVENTIS US
Org Code : 110 55 CORPORATE DR
Priority : 3P BRIDGEWATER, NJ 08807

Stamp Date : 27-JUN-2008 Brand Name : DRONEDARONE HCL
PDUFA Date : 30-APR-2009 Estab. Name:
Action Goal : Generic Name: DRONEDARONE HCL
District Goal: 26-FEB-2009 Dosage Form: (TABLET)
Strength : 400 MG

FDA Contacts: R. FORTNEY Project Manager 301-796-1068
D. LU Review Chemist (HFD-150) 301-796-2059
K. SRINIVASACHAR Team Leader 301-796-1760

Overall Recommendation: ACCEPTABLE on 27-APR-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment : CFN : (b) (4) FEI : (b) (4)
(b) (4)
(b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile : (b) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-DEC-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: (b) (4)

Profile : (b) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-APR-09

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610672 FEI : 3002807193

SANOFI AVENTIS PHARMA SA

69583

NEUVILLE-SUR-SAONE 69583, LYON, FR

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE LABELER

DRUG SUBSTANCE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORTDRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-AUG-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9610721 FEI : 1463
SANOFI AVENTIS PHARMA SA
63480
VERTOLAYE, , FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MICRONIZER
DRUG SUBSTANCE PACKAGER

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-FEB-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1931809 FEI : 1000117606
SANOFI AVENTIS US LLC
6239 LEMAY FERRY RD
SAINT LOUIS, MO 631292805

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-AUG-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9612650 FEI : 3002808206
SANOFI CHIMIE
45 CHEMIN DE METELINE
SISTERON, , FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-APR-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611342 FEI : 3002808208
SANOFI WINTHROP INDUSTRIE
1, RUE DE LA VIERGE
AMBARES ET LAGRAVE, , FR

DMF No: AADA:

FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile	:	TCM	OAI Status:	NONE
Last Milestone:		OC RECOMMENDATION		
Milestone Date:		27-APR-09		
Decision	:	ACCEPTABLE		
Reason	:	DISTRICT RECOMMENDATION		

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/s/

Donghao Lu
4/28/2009 09:35:14 AM
CHEMIST

Ramesh Sood
4/28/2009 10:21:27 AM
CHEMIST



NDA 22-425

**MULTAQ (Dronedarone)
Tablet
400 mg**

Sanofi Aventis

Division of Cardio-Renal Drug Products

Donghao (Robert) Lu, Ph.D.

**Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S. DRUG SUBSTANCE.....	10
P. DRUG PRODUCT	27
A. APPENDICES	N/A
R. REGIONAL INFORMATION	N/A
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	40
A. Labeling & Package Insert	40
B. Environmental Assessment Or Claim Of Categorical Exclusion	N/A
III. Establishment Evaluation Report.....	N/A
IV. List Of Deficiencies.....	N/A



Chemistry Review Data Sheet

1. NDA 22-425
2. REVIEW NUMBER: 1
3. REVIEW DATE: 15 AUGUST 2008
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS

NDA 21-913

DOCUMENT DATE

10 JUNE 2005

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED

NDA 22-425

NDA 22-425

(Amendment: Revised Proposed Labeling)

DOCUMENT DATE

27-JUNE-08

13-FEB-09

7. NAME & ADDRESS OF APPLICANT:

NAME:

Sanofi-Aventis U.S. LLC

ADDRESS:

55 Corporate Drive, Bridgewater, NJ 08807

REPRESENTATIVE:Jon Villaume, Ph.D. Vice President, Regulatory
Development, Corporate Regulatory Affairs**TELEPHONE:**

610-889-6852



CHEMISTRY REVIEW



Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	MULTAQ (Dronedarone)
NON-PROPRIETARY NAME (USAN)	Dronedarone Hydrochloride
CODE NAME/ NUMBER (ONDC ONLY)	SR33589B
CHEMISTRY TYPE / SUBMISSION PRIORITY	1P

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Anti-Arrhythmic

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

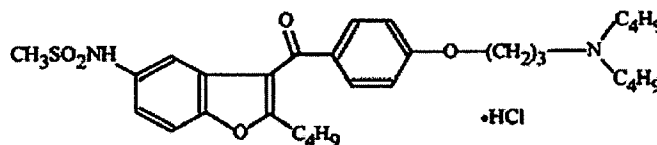
14. R_x/OTC DISPENSED: x R_x OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed
 x Not a SPOTS product

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

Name (USAN): Dronedarone hydrochloride
Name (CAS): Methanesulfonamide, N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-, monohydrochloride
(CAS) Registry Num:
Structural Formula:



Mol. Formula: C₃₁H₄₅ClN₂O₅S
Mol. Wt.: 593.22 g/mol



CHEMISTRY REVIEW



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLET
18409	II	Sanofi Chimie	Drug Substance	1	Adequate	
(b) (4)	III	(b) (4)		4	Adequate	
(b) (4)	III	(b) (4)		4	Adequate	
(b) (4)	III		(b) (4)	4	Adequate	

¹ 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")

² 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
NDA	21-913	Dronedarone Hydrochloride

Note: NDA 21-913 (submitted 10 June 2005) was not approved (action: Not Approvable). NDA 22-425 was submitted to replace NDA 21-913 resubmission. The sponsor incorporated by reference NDA 21-913 and the Complete Response (submitted 27 June 2008) to the 29 August 2006 Action Letter to this New Drug Application 22-425.



CHEMISTRY REVIEW



Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	30-OCT-08	Donghao Lu, Ph.D.
ODS DMETS	N/A *		
EA	N/A *		
Micro Consultation	N/A *		

* see CMC review on NDA 21-913



The Chemistry Review for NDA 22-425

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product MULTAQ (Dronedarone) film-coated tablet, 400 mg, is pending for approval from a CMC perspective. All CMC related issues had been resolved for this application. At the time of writing this review, the office of compliance had not provided a final recommendation for the manufacturing sites in EES. Because of this pending issue, a final recommendation from CMC perspective is not made. The CMC reviewer will file a final memorandum in DFS once the recommendation from the office of compliance is received.

The sponsor should also make changes on the labels:

- (1) The established name should be "Dronedarone" to match the 400 mg strength.
- (2) Add word "Tablets" in association with the established name, out side of the parenthesis.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is dronedarone hydrochloride.

Updated information on the drug substance was provided in this NDA and in DMF No. 18409. The DMF was reviewed and found to be adequate (review dated 10-Dec-2008). It is noted that the drug substance section of the dronedarone hydrochloride was originally provided for NDA 21-913. Additional information can be found in the original CMC reviews for NDA 21-913 and DMF No. 18409.

The drug substance section of the dronedarone hydrochloride in NDA 21-913, initially submitted on June 10, 2005 and subsequently amended with updated stability on December 6, 2005, was further amended with updated CMC information. Only those portions with modifications were provided in this submission and they are evaluated as follows.



Chemistry Assessment Section

Dronedarone hydrochloride has a molecular formula of $C_{31}H_{45}ClN_2O_5S$ and a relative molecular mass of 593.22 g/mol. The salt / base ratio is 1.065. The synthesis route for dronedarone hydrochloride drug substance was presented in NDA 21-913 in two flow charts: (1) synthesis route to (b) (4) from main starting materials; and (2) synthesis route to the drug substance from (b) (4). The structure of dronedarone hydrochloride was elucidated by elemental analysis, ultraviolet spectrometry, infrared spectrometry, nuclear magnetic resonance spectrometry and mass spectrometry. Information for the impurities was provided early with some updated information in this submission.

Dronedarone hydrochloride, was subjected to heat, heat and moisture, light stress, and chemical stress. The drug substance was physically and chemically stable based on evaluation of the testing data. Updated information on drug substance stability (tested for 36 months at 30°C/65%RH and 6 months at 40°C/75%RH) was provided. The data showed that dronedarone hydrochloride drug substance was stable during the test period and further supported the retest period of (b) (4).

2. Drug Product

The drug product is dronedarone hydrochloride 400 mg (base equivalent) immediate release film-coated tablets. The drug product section of the dronedarone hydrochloride was originally provided in NDA 21-913. In this submission, only those portions with modifications were provided and they are evaluated as follows. Additional information can be found in CMC reviews for NDA 21-913.

The tablet is white film-coated oblong tablet with "4142" engraved on one side and a double wave marking on the other. All of the excipients used in the formulation are pharmacopoeial materials and, as such, are tested against the relevant pharmacopoeial monographs. The drug product manufacturing process, (b) (4), was evaluated early in NDA 21-913. The in-process control tests, which ultimately determine the quality of the drug product, are performed at the following steps in the manufacturing program: (b) (4)

The primary packaging components for dronedarone hydrochloride tablets are (b) (4) Aluminum blister packs and (b) (4) bottles. CMC information to support the 100, 200 and 500 mL (b) (4) bottles, replacing the (b) (4) bottles described in the original NDA, were provided. The stability studies of dronedarone hydrochloride 400 mg film-coated tablets, packaged in the (b) (4) bottles, were provided in this submission, including both primary stability study results and stability results supporting the new container closure system. The stability data supported the proposed expiration period (shelf life) of 36 months.

**Chemistry Assessment Section****B. Description of How the Drug Product is Intended to be Used**

The drug product MULTAQ (dronedaron hydrochloride) Tablets, 400 mg is indicated for rhythm and rate control in patients with atrial fibrillation (AF) or atrial flutter, in order to maintain normal sinus rhythm or to decrease ventricular rate. AF is a disorder found in about 2.2 million Americans. In it the heart's two small upper chambers (the atria) quiver instead of beating effectively. As a result, blood may pool and clot. Translocation of the clot to an artery in the brain results in a stroke. Stroke occurs in about 15 percent of the individuals that have AF. The likelihood of developing AF increases with age; three to five percent of people over 65 have atrial fibrillation. Multaq is a prescription medicine used in adults to help control these illnesses. Multaq can lower the risk for having to go into the hospital for heart problems or the risk for death.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Sanofi Aventis has submitted sufficient and appropriate information to support the approval of the drug product. It should be noted that most of the CMC issues were resolved in NDA 21-913, except one CMC concern that an acceptance criterion for (b) (4) should be listed in addition to the current (b) (4) criterion. In this submission, the resolution to this CMC concern was provided. In addition, other updated information were also provided. Based on this review, all CMC related issues had been resolved.

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

Donghao Lu
2/18/2009 01:56:12 PM
CHEMIST

Ramesh Sood
2/18/2009 03:32:57 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	21-913
Applicant:	Sanofi-Aventis
Letter Date:	27 June 2008
Stamp Date:	27 June 2008
PDUFA Date:	27 Dec. 2008
Tradename:	Multaq
Established Name:	Dronedarone
Dosage Form:	Tablets, 400 mg
Route of Administration:	Oral
Indication:	Reduction in risk of cardiovascular hospitalization or death in patients with atrial fibrillation or flutter
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This is a complete response resubmission of the original NDA which received a 'Not Approvable' action on 29 Aug. 2006 for clinical reasons. There were relatively minor CMC issues listed in the action letter concerning the acceptance criteria for drug substance particle size and drug product dissolution. Sanofi has responded to these and, in addition, has provided updated drug substance and drug product information. The DMF 18409 has also been amended. The container closure system for the drug product has been changed based on a comparability protocol submitted in the original NDA. These updates as well as the responses to the CMC questions in the action letter will need an in-depth review.

Labeling

The established name should be 'dronedarone' and not 'dronedarone hydrochloride' to match the dosage form strength.

Comments and Recommendations

The application is fileable. Facilities, original as well as new ones identified in the resubmission, will be entered into EES and the reviewer should verify the accuracy and completeness of the entries. The CMC reviewer who reviewed the original NDA is recommended for this application.

Kasturi Srinivasachar
Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
Branch Chief

July 3, 2008
Date
July 3, 2008
Date

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/s/

Kasturi Srinivasachar
7/3/2008 12:03:42 PM
CHEMIST

Ramesh Sood
7/7/2008 07:47:44 AM
CHEMIST

NDA 21-913

MULTAQ® (Dronedarone) Tablets, 400 mg

Sanofi Aventis

REVIEW #2

Donghao R. Lu, Ph.D.
(Drug Substance Reviewer)

William C. Timmer, Ph.D.
(Drug Product Reviewer)

Division of Cardio-Renal Drug Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Substance and Drug Product.....	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature	11
B. Endorsement Block.....	11
C. CC Block.....	11
Chemistry Assessment	12
I. Review of CTD - Module 3: Quality: Body Of Data: Drug Substance/Product	12

Chemistry Review Data Sheet

1. **NDA 21-913**

2. **REVIEW NUMBER:** 2

3. **REVIEW DATE:** 7 April 2006

4. **REVIEWER:** Donghao R. Lu, Ph.D. Drug Substance
William C. Timmer, Ph.D. Drug Product

5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
IND 49, 484	26 December 1995

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 21-913	10 June 2005

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	Sanofi Aventis
ADDRESS:	11 Great Valley Parkway; Malvern, PA, 19355.
REPRESENTATIVE:	Douglas A. Greene, M.D.
TELEPHONE:	610-889-6425

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	None
NON-PROPRIETARY NAME (USAN)	Dronedarone Hydrochloride
CODE NAME/ NUMBER (ONDC ONLY)	SR33589B
CHEMISTRY TYPE / SUBMISSION PRIORITY	3 S

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Anti-Arrhythmic

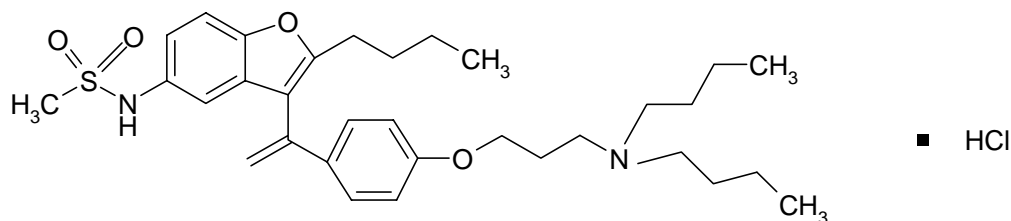
11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: ☒ R_x ☐ OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)☐ SPOTS product – Form Completed☒ Not a SPOTS product

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



Name (USAN):	Dronedarone hydrochloride
Name (CAS):	methanesulfonamide, N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-, monohydrochloride
Molc. Formula:	C ₃₁ H ₄₅ ClN ₂ O ₅ S
Molc. Wt.:	593.22 g/mol

Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
18409	II	Sanofi Chimie	Drug Substance	1	Adequate	10-JAN-06

¹ 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")

² 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
IND	48,484	Dronedarone HCl

Executive Summary Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-MAR-06	J.M. D'Ambrogio
Methods Validation	-- to be initiated --	----	W.C. Timmer, Ph.D.
ODS DMETS	Acceptable	28-OCT-05	J. Jahng, Pharm.D.
EA	FONSI	29-MAR-06	B. Nguyen, Ph.D.

The Chemistry Review for NDA 21-913

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Multaq (Dronedaron HCl) Tablets, 400 mg is recommended as APPROVABLE from a CMC perspective.

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

There are no Phase IV commitments.

The sponsor has included a *Comparability Protocol* which involves packaging components. This protocol has been reviewed and found to be acceptable.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is dronedarone hydrochloride.

Detailed information on the drug substance was provided in DMF No. 18409. The DMF was reviewed and found to be adequate (review dated 10-Jan-2006).

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined.

The synthesis routes and the use of reagents appear adequate.

The impurities detected during the synthesis and development of the DS were evaluated. Analytical methods were developed for the control of the impurities listed above. These methods were briefly described in the tables containing the

Executive Summary Section

previous methods and the current methods.

Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level were presented and described in the review of the DMF.

Dronedarone hydrochloride, was subjected to heat, heat and moisture, light stress, and chemical stress. The DS was physically and chemically stable based on evaluation of the testing data. In addition, the DS appears stable under the storage condition of 30°C/65% RH for 9 months for primary batches and 48 months for supporting batch.

2. Drug Product

The drug product is dronedarone hydrochloride 400 mg¹ (base equivalent) immediate release film-coated tablets.

Dronedarone is active by an oral route. Therefore, (b) (4) tablet dosage forms were formulated for use. The (b) (4) were used for Phase 1 and 2A clinical trials, while the film-coated tablets were used for Phase 2B and 3 clinical trials. For reference, bioavailability between the film-coated tablets used for Phase 2B and the film-coated tablets used for Phase 3 studies has been established; refer to Section 2.7 Biopharmaceutics.

The commercial DP is a finished tablet that has a white film-coat. The tablet is oblong and engraved with « 4142 » code on one side and with a double wave marking on the other side.

All of the excipients used in the formulation are pharmacopoeial materials and, as such, are tested against the relevant pharmacopoeial monographs.

The DP manufacturing process, (b) (4), has been evaluated in this review. The quality of the DP is controlled by verifying the batch number and weight of each component. All materials used are tested and released as per standard practices prior to use. The manufacturing rooms are verified and inspected to be clean and acceptable for use and only materials required for specific operation are in the production area.

The in-process control tests, which ultimately determine the quality of the DP, are performed at the following steps in the manufacturing program: (b) (4)

¹ The drug product contains 426 mg of dronedarone hydrochloride which corresponds to 400 mg dronedarone base.

Executive Summary Section

Again, comprehensive details of the process are available in the manufacturing development report in the submission.

All manufacturing operations are performed in compliance with current GMPs.

The batch size of the DP is typically (b) (4) film-coated tablets.

Appropriate analytical tests and specifications have been developed and appropriately validated. Details of the validation studies are available in the submission.

The results obtained from analysis of the clinical and primary stability batches during the accelerated, long-term, and photostability studies indicate that the impurities or degradation products do not arise from the DP itself.

The primary packaging components for dronedarone hydrochloride tablets are (b) (4) blister packs and (b) (4) bottles. The (b) (4) blister packs are composed of a rigid, transparent, colourless (b) (4) foil of 20 µm thickness.

The 75 ml and 200 ml square white opaque (b) (4) bottles are closed with a child-proof tamper-proof (b) (4) screw cap. The 500 ml rectangular white opaque (b) (4) bottle is closed with a tamper-proof (b) (4) push-fit cap.

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

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AF is a disorder found in about 2.2 million Americans. In it the heart's two small upper chambers (the atria) quiver instead of beating effectively. As a result, blood may pool and clot. Translocation of the clot to an artery in the brain results in a stroke. Stroke occurs in about 15 percent of the individuals that have AF. The likelihood of developing AF increases with age; three to five percent of people over 65 have atrial fibrillation.

There are three major goals of medical treatment of AF: the restoration of normal sinus rhythm, control of the ventricular rate during AF, and prevention of blood clot formation.

Restoration of Sinus Rhythm: Sinus rhythm is often restored with medications by slowing the conduction of electrical impulses, decreasing the excitability and

Executive Summary Section

automaticity of cardiac cells, or prolonging the refractory period of cardiac tissue. Several medications may be used to terminate AF including procainimide (Pronestyl), quinidine, disopyramide (Norpace), amiodarone (Cordarone), and dofetilide (Tikosyn).

Control of Ventricular Rate: To effectively reduce the symptoms associated with AF, it is important that the ventricular rate be controlled. The irregular, flopping sensation in the chest is from the irregular ventricular beat in response to AF. Thus, the faster the ventricles go, the more symptomatic patients usually become. The goal of medications such as beta blockers, calcium channel blockers, and digoxin is to slow down the heart rate by decreasing the excitability of the cardiac cells.

Prevention of Blood Clot Formation: During AF the atria lose their organized pumping action and fibrillate (quiver) in response to the continuous electrical stimulation. In normal sinus rhythm, the atria contract, the valves open and blood fills the ventricles (the lower chambers). The ventricles then contract to complete the organized cycle of contraction that occurs with each heartbeat.

Since the atria *don't* contract during AF, the blood is not able to empty efficiently from the atria into the ventricles with each heartbeat. Blood can then pool and become stagnant in the atria, creating a site for blood clot formation. Since the left side of the heart pumps the oxygenated blood to all parts of the body, clot formation in the left atrium can become a primary source of stroke in patients with AF.

Other current treatment options for AF include medications, electrical cardioversion, ablations, pacemakers, and surgery. The choice of therapy is quite individualized and is usually based on the degree of disability and symptoms associated with the AF.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Sanofi Aventis has submitted sufficient and appropriate information to support an APPROVABLE recommendation for the drug product.

The principal CMC issue involves the particle size distribution. In particular, the drug substance reviewer R. Lu, Ph.D., has submitted the following information request to the sponsor:

In order to better define and control the drug substance particle size distribution please add an acceptance criterion for (b) (4) in addition to the current (b) (4) criterion, or justify why it is not necessary to have an acceptance criterion for (b) (4).

Executive Summary Section

At present, this is the only outstanding CMC issue.

Aside from above, the physical and chemical characteristics, impurity profile, and stability for dronedarone hydrochloride tablets are adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the HPLC assay provides an acceptable degree of separation of dronedarone impurities and degradants. Based on analysis of the stability data, the approved shelf life for Multaq (drodenarone) Tablets, 400 mg is 18 months at room temperature when protected from light.

III. Administrative**A. Reviewer's Signature**

\s\ Robert Lu, Ph.D.

\s\ William C. Timmer, Ph.D.

B. Endorsement Block

R. Sood, Ph.D. / 7-APR-06

Donghao R. Lu, Ph.D. / 7-APR-06

William C. Timmer, Ph.D. / 7-APR-06

C. CC Block

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/s/

William Timmer
4/7/2006 12:41:49 PM
CHEMIST

Ramesh Sood
4/7/2006 02:33:41 PM
CHEMIST

NDA 21-913

MULTAQ® (Dronedarone) Tablets, 400 mg

Sanofi Aventis

Donghao R. Lu, Ph.D.
(Drug Substance Reviewer)

William C. Timmer, Ph.D.
(Drug Product Reviewer)

Division of Cardio-Renal Drug Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE [Dronedarone Hydrochloride, Sanofi Aventis]	12
P DRUG PRODUCT [Dronedarone Hydrochloride, Tablets]	59
A APPENDICES	84
R REGIONAL INFORMATION	84
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	88
A. Labeling & Package Insert	88
B. Environmental Assessment Or Claim Of Categorical Exclusion	90
III. List Of Deficiencies To Be Communicated.....	95

Chemistry Review Data Sheet

1. **NDA 21-913**

2. **REVIEW NUMBER:** 1

3. **REVIEW DATE:** 1 September 2005

4. **REVIEWER:** Donghao R. Lu, Ph.D. Drug Substance
William C. Timmer, Ph.D. Drug Product

5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
IND 49, 484	26 December 1995

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 21-913	10 June 2005

7. **NAME & ADDRESS OF APPLICANT:**

NAME:	Sanofi Aventis
ADDRESS:	11 Great Valley Parkway; Malvern, PA, 19355.
REPRESENTATIVE:	Douglas A. Greene, M.D.
TELEPHONE:	610-889-6425

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	None
NON-PROPRIETARY NAME (USAN)	Dronedarone Hydrochloride
CODE NAME/ NUMBER (ONDC ONLY)	SR33589B
CHEMISTRY TYPE / SUBMISSION PRIORITY	3 S

9. LEGAL BASIS FOR SUBMISSION: 505(b)1

10. PHARMACOL. CATEGORY: Anti-Arrhythmic

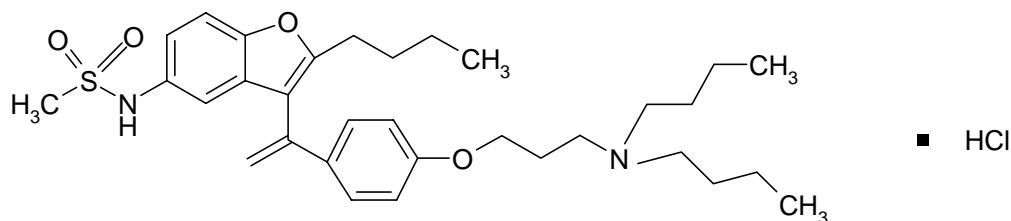
11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: ☒ R_x ☐ OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)☐ SPOTS product – Form Completed☒ Not a SPOTS product

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



Name (USAN):	Dronedarone hydrochloride
Name (CAS):	methanesulfonamide, N-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-, monohydrochloride
Molc. Formula:	C ₃₁ H ₄₅ ClN ₂ O ₅ S
Molc. Wt.:	593.22 g/mol

Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
18409	II	Sanofi Chimie	Drug Substance	1	Adequate	10-JAN-06

¹ 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")

² 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
IND	48,484	Dronedarone HCl

Executive Summary Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-MAR-06	J.M. D'Ambrogio
Methods Validation	-- <i>to be initiated</i> --	----	W.C. Timmer, Ph.D.
ODS DMETS	Acceptable	28-OCT-05	J. Jahng, Pharm.D.
EA	-- <i>submitted; in progress</i> --	10-JUN-05	F. Zielinski, Ph.D.

The Chemistry Review for NDA 21-913

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Multaq (Dronedaron HCl) Tablets, 400 mg is recommended as APPROVABLE from a CMC perspective.

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

There are no Phase IV commitments.

The sponsor has included a *Comparability Protocol* which involves packaging components. This protocol has been reviewed and found to be acceptable.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is dronedarone hydrochloride.

Detailed information on the drug substance was provided in DMF No. 18409. The DMF was reviewed and found to be adequate (review dated 10-Jan-2006).

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined.

The synthesis routes and the use of reagents appear adequate.

The impurities detected during the synthesis and development of the DS were evaluated. Analytical methods were developed for the control of the impurities listed above. These methods were briefly described in the tables containing the

Executive Summary Section

previous methods and the current methods.

Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level were presented and described in the review of the DMF.

Dronedarone hydrochloride, was subjected to heat, heat and moisture, light stress, and chemical stress. The DS was physically and chemically stable based on evaluation of the testing data. In addition, the DS appears stable under the storage condition of 30°C/65% RH for 9 months for primary batches and 48 months for supporting batch.

2. Drug Product

The drug product is dronedarone hydrochloride 400 mg¹ (base equivalent) immediate release film-coated tablets.

Dronedarone is active by an oral route. Therefore, (b) (4) tablet dosage forms were formulated for use. The (b) (4) were used for Phase 1 and 2A clinical trials, while the film-coated tablets were used for Phase 2B and 3 clinical trials. For reference, bioavailability between the film-coated tablets used for Phase 2B and the film-coated tablets used for Phase 3 studies has been established; refer to Section 2.7 Biopharmaceutics.

The commercial DP is a finished tablet that has a white film-coat. The tablet is oblong and engraved with « 4142 » code on one side and with a double wave marking on the other side.

All of the excipients used in the formulation are pharmacopoeial materials and, as such, are tested against the relevant pharmacopoeial monographs.

The DP manufacturing process, (b) (4), has been evaluated in this review. The quality of the DP is controlled by verifying the batch number and weight of each component. All materials used are tested and released as per standard practices prior to use. The manufacturing rooms are verified and inspected to be clean and acceptable for use and only materials required for specific operation are in the production area.

The in-process control tests, which ultimately determine the quality of the DP, are performed at the following steps in the manufacturing program: (b) (4)

¹ The drug product contains 426 mg of dronedarone hydrochloride which corresponds to 400 mg dronedarone base.

Executive Summary Section

Again, comprehensive details of the process are available in the manufacturing development report in the submission.

All manufacturing operations are performed in compliance with current GMPs.

The batch size of the DP is typically (b) (4) film-coated tablets.

Appropriate analytical tests and specifications have been developed and appropriately validated. Details of the validation studies are available in the submission.

The results obtained from analysis of the clinical and primary stability batches during the accelerated, long-term, and photostability studies indicate that the impurities or degradation products do not arise from the DP itself.

The primary packaging components for dronedarone hydrochloride tablets are (b) (4) blister packs and (b) (4) bottles. The (b) (4) blister packs are composed of a rigid, transparent, colourless (b) (4) foil of 20 µm thickness.

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Executive Summary Section

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Executive Summary Section

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\s\ Robert Lu, Ph.D.

\s\ William C. Timmer, Ph.D.

B. Endorsement Block

R. Sood, Ph.D. / 14 Mar-06

Donghao R. Lu, Ph.D. / 01-MAR06

William C. Timmer, Ph.D. / 01-MAR-06

C. CC Block

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

/s/

William Timmer
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CHEMIST

Ramesh Sood
3/17/2006 01:25:19 PM
CHEMIST