CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-993

CHEMISTRY REVIEW(S)

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	21-993
Applicant:	Schering-Plough HealthCare Products
Stamp Date:	Feb. 13, 2006
PDUFA Date:	Dec. 13, 2006
Trademark:	Claritin RediTabs® 12 Hour Tablets
Established Name:	Loratadine 5 mg
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Allergic rhinitis
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

A. Summary

Schering-Plough HealthCare Products (SPHCP) is submitting a 505(b) (1) New Drug Application (NDA) for Claritin RediTabs® 12 Hour Tablets, 5 mg with proposed labeling for OTC marketing. The proposed indication is allergic rhinitis, and the listed reference drug is Clartin® D12 Extended Release Tablets (NDA 19-670).

The applicant references DMFs 6626 and 13032 for the drug substance, loratadine USP. The two DMFs have been reviewed multiple times for multiple approved products, most recently in April 2006, and found adequate. [redacted] micronized loratadine is used in the manufacture of drug product. The micronization process has been included in the DMFs and their reviews.

The proposed drug product is an orally disintegrating tablet packaged in [redacted] blister packs. The formulation contains the following excipients: gelatin NF, mannitol USP, Flavor Mint [redacted], anhydrous citric acid USP [redacted] All excipients are USP/NF grade materials except Flavor Mint [redacted] which is referenced to DMF [redacted]

It should be noted that the proposed formulation is identical to that of the approved drug product Claritin 10 mg Orally Disintegrating Tablets (NDA 20-704) with the exception of a lower drug strength. The proposed drug product manufacturing process is also the Zydis® technology approved in NDA 20-704.

The to-be-marketed formulation is the same formulation used in the BE/BA (bioequivalent/bioavailability) studies and registration stability batches. Stability data provided

in the initial submission to support an expiry period of 24 months at a controlled room temperature of 68-77°F (20-25°C) include 12 months at 25°C/60% RH and 30°C/65% RH, and 6 months at 40°C/75% RH from three pilot-scale [redacted] batches. The pilot scale is approximately [redacted] of the production scale depending on the number of count per blister card.

B. Critical issues for review

No critical review issues have been identified. This is because all important CMC aspects of this NDA are either identical or very similar to the approved NDA 20-704 (Claritin 10 mg Orally Disintegrating Tablets). For example, both NDAs reference to the same drug substance DMFs, and use the same manufacturing process, the Zydis® technology, for drug product manufacture. The formulation of this NDA is identical to that of NDA 20-704 with the exception of a lower drug strength. The drug product specification is very similar to that of NDA 20-704.

Although some portion of the stability section (p. 18 of 18, 3.2.P.8.1) may appear to suggest that the proposed container/closure system [redacted] blister pack) is different from that approved in NDA 20-704, the [redacted] blister pack has actually been approved for NDA 20-704 through Supplement SCP-001 in 1998.

Regarding GMP Inspection, both the drug substance and drug product manufacturing sites are located overseas. The drug substance sites are located in Ireland and Singapore. The drug product manufacturing site is located in the United Kingdom. GMP inspection requests will be submitted shortly after the filing meeting.

C. Comments for 74-Day Letter

None.

D. Recommendation:

This NDA is fileable from a CMC perspective.

Shulin Ding
Pharmaceutical Assessment Lead

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. **Drug Substance** Referenced to DMFs 6626 and 13032.

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

2. **Drug Product**

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/s/

Shulin Ding
4/7/2006 03:20:48 PM
CHEMIST

Moo-Jhong Rhee
4/7/2006 03:38:48 PM
CHEMIST
Chief, Branch III

Chemistry Review Data Sheet

NDA 21-993

CLARITIN® REDITABS 12 HOURS TABLETS
(loratadine tablet, 5 mg)
Schering – Plough HealthCare Products
Division of Nonprescription Drug Products

Tarun Mehta, M.Sc.

ONDQA Pre Approval Marketing Division II, Branch III

Chemistry Review Data Sheet

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 21-993

2. REVIEW #: 1

3. REVIEW DATE: 29-November-2006

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWS:

Submission(s) Reviewed	Document Date
ORIGINAL	10-FEB-2006
Amendment	6-OCT-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering-Plough HealthCare Products
Address:	556 Morris Ave Summit, NJ 07901
Representative:	Doreen Frank, Director Regulatory Affairs
Telephone:	908-473-1655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Claritin RediTabs 12 Hours Tablets
b) Non-Proprietary Name (USAN): Loratadine
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Orally Disintegrating Tablets (ODT)

12. STRENGTH/POTENCY: 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X_ OTC

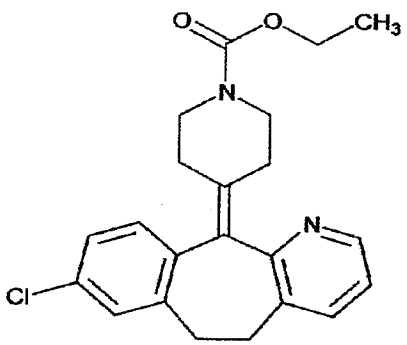
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name: 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo [5, 6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester.

Chemical Structure:



Molecular weight: 382.88
Molecular formula: $C_{22}H_{23}ClN_2O_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
6626	II	Schering-Plough Co. Rathdrum, Ireland	Loratadine drug substance	1	Adequate	14-APR-2006	Reviewed for N 21-891 by Tarun Mehta
13032	II	Schering-Plough Co. Singapore	Loratadine drug substance	1	Adequate	14-APR-2006	Reviewed for N 21-891 by Tarun Mehta
[redacted]				3	Adequate	21-APR-2005	Reviewed for N [redacted]
				3	Adequate	27-APR-2006	Reviewed for N [redacted] by Fraser Blair
				3	Adequate	27-APR-2006	Reviewed for N [redacted] by Fraser Blair

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF is not review, 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)

18. STATUS:

ONDQA:

CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMETS	NA		
EES	Acceptable	25-AUG-2006	S. Adams (HFD-322)

Chemistry Assessment Section

The Chemistry Review for NDA 21-993

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Control, and Manufacturing standpoint, this NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

None

II. Summary of Chemistry Assessments

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

Claritin 5mg orally disintegrating tablet delivered (ODT) 5mg of Loratadine drug. Proposed 5mg ODT dosage is identical to approved 10mg ODT in every aspect of formulation, manufacturing and packaging. Formulation differs in amount of drug to excipient ratio. Approved 10mg contain —w/w drug concentration where as proposed 5mg dosage has —w/w drug concentration. Loratadine is used for the treatment of allergic rhinitis and chronic idiopathic urticaria. The dose for adult and children age 6 years and over is one 5mg ODT every 12 hours.

Proposed orally disintegrating tablet (ODT) formulation is a unique oral solid dosage form compared to traditional tablet. Drug product manufacturer Cardinal Health care used their patented technology called Zydis® products for orally disintegrating tablet (ODT) manufacturing. Manufacturing of ODT

The manufacturing process is controlled by in-process acceptance criteria and specifications. Proposed in-process specifications are found adequate. Critical attributes

such as [redacted] were monitored during the process.

The drug product packaged in proposed marketing container/closure system and kept for 12 months at long-term and intermediate stability condition showed no significant changes in drug quality. Data support the proposed expiration period of 24 months.

Schering Corporation, Ireland, manufactures drug substance Loratadine. The Chemistry, Manufacturing and Control information of the drug substance is described in Schering's DMF 6626 and 13032 and deemed adequate to support the NDA. DMF 6626 and 13032 were reviewed on April 14, 2006 and found adequate.

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

The recommended dosing schedule for CLARITIN 5mg Orally Disintegrating tablet is one ODT tablet every twelve hours for adults and children 6 years and over.

The drug product storage condition is between 20-25^{0}C (68 – 77^{0}F).

C. Basis for Approvability

- Review of original submissions of this NDA 21-993 found satisfactory.
  - The chemistry deficiency regarding revision of specification to add disintegration test was corrected in the amendment dated 24-OCT-2006.
  - All other aspect of drug product quality was controlled adequately.
  - Stability data support quality of drug product for its expiry date.
- The final recommendation from the Office of Compliance for the drug product-manufacturing site is **ACCEPTABLE (see Attachment–1)**.

III. Administrative

A. Reviewer's Signature: Electronically entered in the DFS

46 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Tarun Mehta
11/29/2006 01:45:43 PM
CHEMIST

Moo-Jhong Rhee
11/29/2006 03:14:41 PM
CHEMIST
Chief, Branch III