CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-556Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-556

Carbinoxamine ER Oral (b) (4)

Tris Pharma

Julia C. Pinto, Ph.D.

Office of New Drug Quality Assessment, Division III

Division of Pulmonary, Allergy and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 22-556

2. REVIEW #: 2

3. REVIEW DATE: January 5, 2013

4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-07-2010
Amendment	12-29-2010
Amendment	01-20-2011
Amendment	04-14-2011
Amendment	06-03-2011
Amendment	06-10-2011
Amendment	06-24-2011
Amendment	06-30-2011
Amendment	07-14-2011
Amendment	08-12-2011
Amendment	08-19-2011

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	October 5, 2012
Amendment	October 17, 2012
Amendment	December 7, 2012
Amendment	January 9, 2013
Amendment	February 15, 2013

7. NAME AND ADDRESS OF APPLICANT:

Name: Tris Pharma
Address: 2033 Route 130, Suited
Monmouth Junction, NJ 08852
Telephone: 732-940-0358

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Karbinal ER™

b) Non-Proprietary Name: Carbinoxamine Maleate USP
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: §505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Seasonal and Perennial Allergic Rhinitis

11. DOSAGE FORM: Extended Release Oral Suspension

12. STRENGTH/POTENCY: 4mg /5ml (b) (4) mg carbinoxamine (b) (4) equivalent to 4 mg carbinoxamine maleate)

13. ROUTE OF ADMINSITRATION: Oral

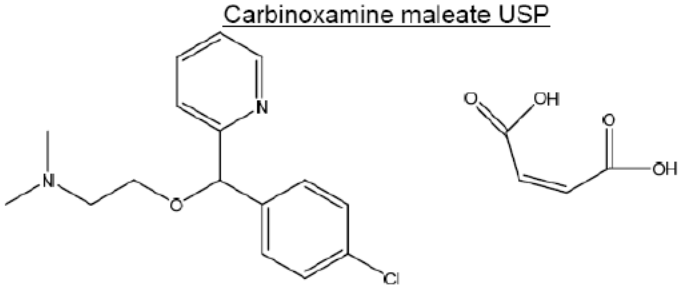
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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:

Carbinoxamine maleate USP



IUPAC name: 2-[(4-chlorophenyl)-2-pyridinyl-methoxy)-N,N-dimeythylethanamine (Z)-2-butenedioate (1:1)

Molecular formula: $C_{16}H_{19}ClN_2O$. $C_4H_4O_4$
Relative molecular weight 406.86 (maleate). (b) (4)

Chemistry Review Data Sheet

A. DMFs:

B.

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE REVIEW COMPLETED	COMMENTS
DMF (b) (4)	II	(b) (4)	Carbinoxamine Maleate	1	adequate	July 22, 2011	Chem Rev #1 by Ted Carver (3/3/2011). Second review by J. Pinto (7/22/2011)
DMF (b) (4)	II		(b) (4)	3	adequate	April 2011	Neeru Takiar,
DMF (b) (4)	II			3	Adequate	Sept 1999	A. Mitra
DMF (b) (4)	V			1	Adequate	September 2011	Asoke Mukherjee
DMF (b) (4)	IV			3	Adequate	Nov. 20, 2009	A. Mitra
DMF (b) (4)	III			3	Adequate	Nov 23, 2009	A. Mitra
DMF (b) (4)	III			1	Adequate	August 5, 2011	D. Klein
DMF (b) (4)	III			4			
DMF (b) (4)	III			4			
DMF (b) (4)	III			4			
DMF (b) (4)	III			4			
DMF (b) (4)	III			4			
DMF (b) (4)	III			3	Adequate	Nov 22 2002	G. Lunn
DMF (b) (4)	III			1	Adequate	August 26, 2011	D. Klein
DMF (b) (4)	III			1	Adequate	August 26, 2011	D. Klein
DMF (b) (4)	III			3	Adequate	Jan. 4, 2010	Zarabi?

[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	102091	Carbinoxamine Maleate

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Adequate	February 4, 2013	Office of Compliance
Pharm/Tox	Adequate	Rev #1	A. Mukherjee
Biopharm (ONDQA)	Adequate	Rev #1	S. Suarez, Ph.D.
Microbiology	Adequate	Review #2	Jessica Cole, Ph.D.
LNC	NA		
Methods Validation	NA		
DMET/DDMAC			
EA	Categorical exclusion satisfactory	8-31-2011	Julia Pinto

The Chemistry Review for NDA 22-556

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Insufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, was provided in original NDA submission. Some deficiencies were observed, in the manufacture, control and packaging of the drug product. A microbiology consult was also requested and several deficiencies were also identified. All deficiencies have been satisfactorily resolved in the resubmission. Further, an overall recommendation from the Office of Compliance, recommends all sites as adequate. Therefore this NDA is recommended for approval.

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

Carbinoxamine maleate drug substance, is a first-generation antihistamine that inhibits the histamine H_1-receptor. The manufacture and control of the drug substance is referenced to DMF (b) (4) and is adequate in support of the drug product (reviewed by Julia Pinto, Ph.D. and Ted Carver, Ph.D.)The API is packaged in (b) (4) and then stored inside an (b) (4) (b) (4). The retest period is (b) (4) The API manufacturer is (b) (4) (b) (4). The Office of Compliance has recommended this site as satisfactory.

The drug product is formulated as a 12-hour extended release suspension indicated for the treatment of allergic rhinitis. The immediate release Carbinoxamine Maleate oral solution (4mg/5ml) marketed by Mikart, is the innovator product and is the reference listed drug (RD) for the development of the ER product. The proposed ER formulation is intended to be comparable to the IR product from Mikart (a concentration of 4 mg/5ml of carbinoxamine maleate) and uses the polistirex drug delivery technology that involves (b) (4) It is assumed that (b) (4) (b) (4) to the polistirex matrix and hence the theoretical concentration is (b) (4) mg of the (b) (4) per 5 mL of the suspension which is equivalent to the 4 mg of carbinoxamine maleate). In the gastrointestinal tract, counter ions penetrate the complex and displace the drug from (b) (4), so that it slowly diffuses from the complex and is then freely absorbed over a longer period of time. The manufacturing process is (b) (4)

(b) (4)

(b) (4)

The DP is manufactured at Tris Pharma in Monmouth Junction, NJ. The Office of Compliance has recommended this site as satisfactory. The drug product is packaged in 1oz physician samples, (b) (4), 300ml and 480ml (b) (4) bottles, stored under recommended conditions of 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) with an expiry of 24 months.

B. Description of How the drug is intended to be used:

Carbinoxamine ER 4 mg/5ml (b) (4) equivalent to carbinoxamine maleate 4 mg/5 mL) oral suspension is an extended release oral suspension of carbinoxamine maleate, an anti-histamine agent indicated for the treatment of allergic rhinitis.

Adults and Adolescents 12 years of age and older (2):
7.5 mL to 20 mL (6 to 16 mg) every 12 hours
Children 2-11 years of age (approximately 0.2 to 0.4 mg/kg/day) (2):
2 to 3 years – 3.75 mL to 5 mL (3 to 4 mg) every 12 hours
4 to 5 years – 3.75 mL to 10 mL (3 to 8 mg) every 12 hours
6 to 11 years – 7.5 mL to 15 mL (6 to 12 mg) every 12 hours

C. Basis for Approvability Recommendation

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA resubmission. Several deficiencies were observed, during the first review cycle, in the manufacture and control of the drug product. These deficiencies have been satisfactorily resolved. This re-submission also provides for a change in dissolution specifications that have been reviewed as satisfactory by the biopharm reviewer (S. Suarez, Ph.D.). Further, an overall recommendation from the office of compliance, for the drug substance and drug product manufacturing sites is recommended as acceptable. Therefore this NDA is recommended for approval from the CMC standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.
Pharmaceutical Assessment Leader: Alan C. Schroeder, Ph.D.
Project Manager: Miranda Raggio, BA, BSN, MA
Branch Chief: Prasad Peri, Ph.D.

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/s/

JULIA C PINTO
03/07/2013

PRASAD PERI
03/08/2013

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22556/000	**Sponsor:**	TRIS PHARMA INC
(:ode:	570		2033 RT 130 STE D
Priority:	3		MONMOUTH JUNCTION, NJ 08852
Stamp Date:	08-DEC-2010	**Brand Name:**	CARBINOXAMINE MALEATE
PDUFA Date:	05-APR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	04-FEB-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SUSPENSION; CARBINOXAMINE MALEATE; 4MG/5ML	

FDA Contacts:	Y. LIU	Project Manager	3017961926
	ID = 144440	Review Chemist	
	A. SCHROEDER	Team Leader	3017961749

Overall Recommendation:	ACCEPTABLE	on 19-NOV-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 06-NOV-2012	by EES_PROD		
	PENDING	on 06-NOV-2012	by EES_PROD		
	PENDING	on 06-NOV-2012	by EES_PROD		
	WITHHOLD	on 11-OCT-2011	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 22-SEP-2011	by EES_PROD		
	WITHHOLD	on 22-SEP-2011	by EES_PROD		
	PENDING	on 10-AUG-2011	by EES_PROD		
	WITHHOLD	on 04-MAY-2011	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	(b) (4)
	(b) (4)		
	(b) (4)		
	(b) (4)		
DMF No:	(b) (4)	**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:** 3004712471	
	TRIS PHARMA INC		
	MONMOUTH JUNCTION, , UNITED STATES 088523003		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
Profile:	SUSPENSIONS AND EMULSIONS (NON PARENTERALS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date October 4, 2011

From Vipul Dholakia, Ph.D.
Compliance Officer
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality

Subject Concurrence with District Withhold Recommendation
NDA 22-556 Carbinoxamine Extended Release Oral Suspension

Thru Dave Doleski, Branch Chief,
New Drug Manufacturing Assessment Branch

To Prasad Peri, Chief, Branch VIII (OPS/ONDQA/DNDQA III/DAAAP)

Applicant: TRIS Pharma Inc.
2033 Route 130, Suite D
Monmouth Junction, NJ 08852

Establishment: TRIS Pharma Inc.
2033 Route 130, Suite D
Monmouth Junction, NJ 08852
FEI: 3004712471

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) conducted from August 08, 2011 to August 16, 2011 at the TRIS Pharma, Inc. facility. DGMPA has also reviewed the firm's August 23, 2011 written response to the FDA Form-483 observations. No further Form-483 responses have been received from the firm since August 23, 2011.

The Division of Good Manufacturing Practice Assessment (DGMPA) concurs with New Jersey District Office's withhold recommendation for NDA 22-556. NWJ-DO recommended withholding approval of this application due to lack of a laboratory or production investigation to evaluate possible root causes of OOS results and failure to report failing test results in the submission to the agency.

- There is no assurance as to the validity of the dissolution test results submitted in the application.
  - (b) (4)

(b) (4)

The firm has committed to take corrective actions and proposed to revise and update SOP F06 "Laboratory Investigations" to include the L1, L2 and L3 acceptance criteria for dissolution results by the end of August 2011. The firm did not provide any documents to show how appropriate investigations would be conducted for the retesting and re-sampling of product when inconsistent or OOS results are obtained. The corrective actions committed to by the firm regarding how to conduct proper investigations should be evaluated in the next inspection.

It remains the firm's responsibility to assure continued compliance with the current good manufacturing practices.

If you have any questions, please contact me at (301) 796-5065.

Vipul Dholakia, Ph.D.

cc:

HFR-CE350	District Pre-Approval Manager (PAM), Karen D'Orazio
HFD-323	NDMAB Team Leader, Tara Gooen
HFD-323	Shared Drive\\cdnas\OCS1\OC_320\HFD-323\Domestic PAI Case management

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/s/

SWATI A PATWARDHAN
10/06/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22556/000	**Sponsor:**	TRIS PHARMA INC
Org. Code:	570		2033 RT 130
Priority:	3		MONMOUTH JUNCTION, NJ 08852
Stamp Date:	08-DEC-2010	**Brand Name:**	CARBINOXAMINE MALEATE
PDUFA Date:	08-OCT-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	09-APR-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; SUSPENSION; CARBINOXAMINE MALEATE; 4MG/5ML

FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	T. CARVER	Review Chemist		301-796-3878
	A. SCHROEDER	Team Leader		301-796-1749

Overall Recommendation:	PENDING	on 22-SEP-2011	by EES_PROD
	WITHHOLD	on 22-SEP-2011	by EES_PROD
	PENDING	on 10-AUG-2011	by EES_PROD
	WITHHOLD	on 04-MAY-2011	by EES_PROD

Establishment:	**CFN:**	**FEI:**	(b) (4)
	(b) (4)		
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	DO RECOMMENDATION		
Milestone Date:	05-OCT-2011		
Decision:	ACCEPTABLE		
Reason:	INSPECTION		

Establishment:	**CFN:** (b) (4)	**FEI:**	(b) (4)
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	20-JAN-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** 3004712471	
	TRIS PHARMA INC. 2033 US HIGHWAY 130 MONMOUTH JUNCTION, NJ 088523003		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE OTHER TESTER		
Profile:	LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-SEP-2011		
Decision:	WITHHOLD		
Reason:	EIR REVIEW-CONCUR W/DISTRICT		

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/s/

SWATI A PATWARDHAN
10/06/2011

NDA 22556

Karbinal ER (Carbinoxamine Maleate) Extended-release Oral suspension
4 mg carbinoxamine per 5 mL
Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Tris Pharma, Inc.
2033 Route 130
Monmouth Junction, NJ 08852

Indication:

- Seasonal and perennial allergic rhinitis
- Vasomotor rhinitis
- Allergic conjunctivitis due to inhalant allergens and foods
- Uncomplicated allergic skin manifestations of urticaria and angioedema
- Dermatographism
- As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled
- Amelioration of the severity of allergic reactions to blood or plasma

Dose
Adults (b) (4) years of age and Older (2):

- 7.5 to 20 mL (6 to 16 mg) every 12 hours

Presentation: The drug product is packaged in (b) (4) with a child resistant cap. Each bottle (b) (4)

EER Status:	Recommendations:	Withhold
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Not recommended
	DMETS-	Acceptable
	Biopharm–	Acceptable
	Microbiology –	Inadequate (comments on Burkholderia cepacia)
	Pharm/toxicology –	Satisfactory

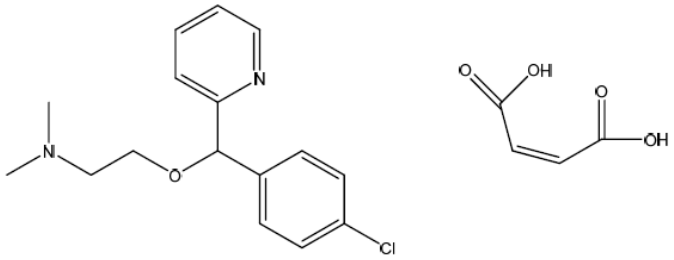
Original Submission: 07-Dec-2010

Post-Approval CMC Agreements: None

Background:
This is a standard NDA with a 10 month clock. The NDA is in electronic format with labeling provided in SPL format. The immediate release formulation is approved and marketed by Mikart, Inc (under the name Palgic®) and is the RLD for this application.

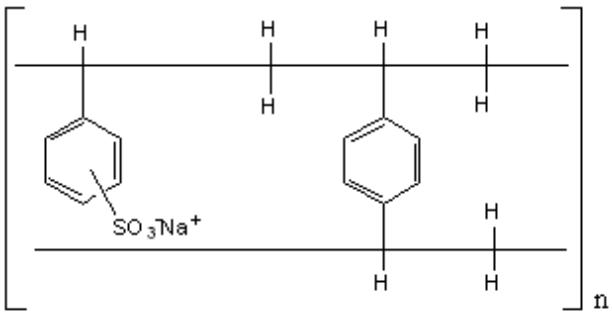
Drug Substance:
Carbinoxamine maleate is a white crystalline powder, and it is a first-generation antihistamine that inhibits the histamine H_1-receptor. It is very soluble in water, freely soluble in alcohol and chloroform and slightly soluble in ether. It has a melting point of 116-121ºC. The chemical name is 2-[(4-chlorophenyl)-2-pyridinylmethoxy]-*N*, N-*dimethylethanamine* (Z)-2-butenedioate (1:1) and its molecular structure and weight are $C_{16}H_{19Cl}N_2O{\cdot}C_4H_4O_4$, MW = 406.86.

Carbinoxamine maleate USP



The manufacture and control of the drug substance is referenced to DMF (b) (4) and is adequate in support of the drug product (reviewed by Julia Pinto, Ph.D. and Ted Carver, Ph.D.). The drug substance is manufactured by (b) (4) The site was found acceptable by the Office of Compliance.

The drug-polistirex complex is formed with the active ingredient (carbinoxamine maleate, USP) and sodium polystyrene sulfonate, USP, which has the following structure:



Specifications which are provided in the NDA for the drug substance epinephrine mostly follow the USP monograph. They include Description, Identification (IR, and UV), Melting range, pH, Loss on Drying, Residue on Ignition, Heavy Metals, Assay, residual Solvents, and Impurities.

The drug substance is packaged in (b) (4) and stored in a (b) (4) container. A retest period of (b) (4) months is assigned.

Conclusion: The drug substance is satisfactory.

Drug Product:
Karbinal ER Extended-Release Oral Suspension, eq. to 4 mg carbinoxamine maleate per 5 mL is supplied as light beige to tan viscous suspension with strawberry banana flavor, containing 4 mg carbinoxamine maleate USP per 5 mL in bottles of (b) (4) Each 5 mL ((b) (4)) of extended-release oral suspension contains 4 mg carbinoxamine maleate and the following inactive ingredients: citric acid anhydrous, flavor, glycerin, high fructose corn syrup, methylparaben, modified food starch, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, and xanthan gum.

The drug product is manufactured by Tris Pharma, Inc., Monmouth Junction, NJ and the office of compliance has provided a **WITHHOLD** recommendation for this site.

The formulation uses the polistirex drug delivery technology that involves the (b) (4) In the gastrointestinal tract, counter ions penetrate the complex and displace the drug from (b) (4), so that it slowly diffuses from the complex and is then freely absorbed over a longer period of time.

(b) (4)

The drug product is controlled by testing for Description, Color, Identification (HPLC and UV), pH, Deliverable Volume, Microbial Limits, Preservative, Assay, Dissolution, Impurities, and (b) (4).

Several deficiencies and clarifications are required from the sponsor with regards to the drug product. They are listed at the end of this review. **They are related to specifications, manufacturing process, control of leachables, updated stability data and development of additional microbial testing methods. It is noted that there is no control of PSD for the final drug product. This will be requested as well.**

Since the drug product is not going to be approved in this review cycle (failed BE study), these deficiencies are being sent to the applicant in the CR letter. These comments by themselves would have otherwise been acceptable as post approval commitments or agreements from a ONDQA perspective.

The drug product is packaged in (b) (4) and it is to be stored under recommended conditions of 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months is proposed.

Conclusion: The drug product is not acceptable and NDA not recommended for approval.

CMC issues that are still pending:

ONDQA deficiencies

1: Clarify if any overages were used in the manufacture of the drug product.

2: Include in-process controls for (b) (4) during mixing of the (b) (4).

3: Update the NDA specifications to include testing for particle size distribution of the drug product at release and stability. Also include a test and acceptance criteria for (b) (4) carbinoxamine at release. Clarify if the labeled strength is based upon the carbinoxamine (b) (4) or the carbinoxamine (b) (4). Clarify if the maleate salt is (b) (4). Revise the drug product specifications accordingly.

4: Provide a response to the August 15, 2011 Information Request that is also shown below. The Agency acknowledges the (b) (4) ppm acceptance criteria of (b) (4) in the (b) (4) USP excipient. Also, we acknowledge the (b) (4) container meeting the USP <661> acceptance criteria of NMT (b) (4) ppm (b) (4). Test the latest time point of each of the stability batches (TB-24A; TB-026A; and TB-027A) for the amount of (b) (4) and for the common impurities of (b) (4) in the drug product.

5: With respect to the alternate container (b) (4) used to package test Batch TB-085A, provide test results at the 24 month time point for (b) (4) and for the common impurities of (b) (4)

6: Revise the stability commitment to state that stability results will be submitted to NDA annual reports.

Microbiology Deficiencies: From Microbiology Review by Jessica Cole, Ph.D. August 31, 2011:

1. The applicant should continue to develop a test method to recover *Burkholderia cepacia* complex organisms potentially present in raw materials and the final product. The test method and revised specification should be submitted in the complete response.

2. Preservative effectiveness testing should be conducted on three batches of drug product.

Office of Compliance deficiency

All drug substance and drug product manufacturing and testing sites will need to have acceptable compliance status prior to an approval.

Overall Conclusion: The NDA is recommended for **Complete Response** from CMC standpoint. No labels are attached as they may be revised.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

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/s/

PRASAD PERI
09/15/2011

NDA 22-556

Carbinoxamine ER Oral (b) (4)

Tris Pharma

Julia C. Pinto, Ph.D.
Donald Klein, Ph.D.

Office of New Drug Quality Assessment, Division III

Division of Pulmonary, Allergy and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 22-556

2. REVIEW #: 1

3. REVIEW DATE: June 17, 2011

4. REVIEWER: Julia C. Pinto, Ph.D.; Donald Klein, Ph.D..

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-07-2010
Amendment	12-29-2010
Amendment	01-20-2011
Amendment	04-14-2011
Amendment	06-03-2011
Amendment	06-10-2011
Amendment	06-24-2011
Amendment	06-30-2011
Amendment	07-14-2011
Amendment	08-12-2011
Amendment	08-19-2011

7. NAME AND ADDRESS OF APPLICANT:

Name: Tris Pharma
Address: 2033 Route 130, Suited
Monmouth Junction, NJ 08852
Telephone: 732-940-0358

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Karbinal ER™
b) Non-Proprietary Name: Carbinoxamine Maleate USP
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: §505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Seasonal and Perennial Allergic Rhinitis

11. DOSAGE FORM: Extended Release Oral Suspension

12. STRENGTH/POTENCY: 4mg /5ml (carbinoxamine maleate)

13. ROUTE OF ADMINSITRATION: Oral

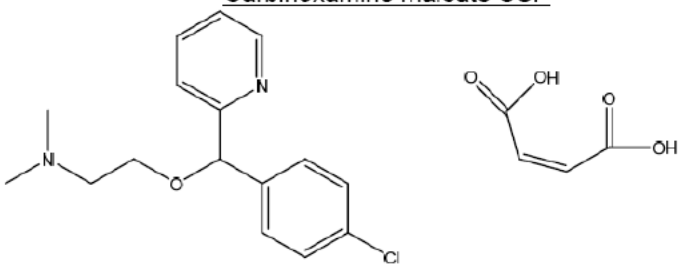
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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:

Carbinoxamine maleate USP



IUPAC name: 2-[(4-chlorophenyl)-2-pyridinyl-methoxy)-N,N-dimeythylethanamine (Z)-2-butenedioate (1:1)

Molecular formula: $C_{16}H_{19}ClN_2O$. $C_4H_4O_4$
Relative molecular weight 406.86 (maleate). (b) (4) ((b) (4)

A. DMFs:

B.

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE REVIEW COMPLETED	COMMENTS
DMF (b) (4)	II	(b) (4)	Carbinoxamine Maleate	1	adequate	July 22, 2011 and	Chem Rev #1 by Ted Carver (3/3/2011). Second review by J. Pinto (7/22/2011)
DMF (b) (4)	II	(b) (4)		3	adequate	April 2011	Neeru Takiar,

DMF (b) (4)	II	(b) (4)	3	Adequate	Sept 1999	A. Mitra
DMF (b) (4)	V		1	Adequate	September 2011	Asoke Mukherjee
DMF (b) (4)	IV		3	Adequate	Nov. 20, 2009	A. Mitra
DMF (b) (4)	III		3	Adequate	Nov 23, 2009	A. Mitra
DMF (b) (4)	III		1	Adequate	August 5, 2011	D. Klein
DMF (b) (4)	III		4			
DMF (b) (4)	III		4			
DMF (b) (4)	III		4			
DMF (b) (4)	III		4			
DMF (b) (4)	III		4			
DMF (b) (4)	III		3	Adequate	Nov 22 2002	G. Lunn
DMF (b) (4)	III		1	Adequate	August 26, 2011	D. Klein
DMF (b) (4)	III		1	Adequate	August 26, 2011	D. Klein
DMF (b) (4)	III		3	Adequate	Jan. 4, 2010	Zarabi

[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	102091	Carbinoxamine Maleate

18. Status

Chemistry Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	August 10, 2011	Office of Compliance
Pharm/Tox	Adequate	Rev #1	A. Mukherjee
Biopharm (ONDQA)	Adequate	Rev #1	S. Suarez, Ph.D.
Microbiology	Inadequate	Review #1	Jessica Cole, Ph.D.
LNC	NA		
Methods Validation	NA		
DMET/DDMAC			
EA	Categorical exclusion satisfactory	8-31-2011	Julia Pinto

The Chemistry Review for NDA 22-556

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA was originally assigned to Ted Carver, Ph.D, a CMC reviewer within ONDQA. However, Dr. Carver, left the Agency midway in the review cycle and this submission was reassigned to Drs. Julia Pinto and Don Klein. Dr. Klein reviewed the drug product container closure system and stability sections of this review. The remainder of the review is prepared by Dr. Pinto.

Insufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. Some deficiencies were observed, in the manufacture, control and packaging of the drug product. A microbiology consult was also requested and several deficiencies remain outstanding. Further, an overall recommendation is pending from the office of compliance, for the drug substance and drug product manufacturing sites wherein the DP site is recommended as a "withhold". Therefore this NDA is recommended as approvable pending the resolution of the deficiencies listed at the end of this review and a satisfactory recommendation from Office of Compliance (OC).

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

Carbinoxamine maleate drug substance, is a first-generation antihistamine that inhibits the histamine H_1-receptor. The manufacture and control of the drug substance is referenced to DMF (b) (4) and is adequate in support of the drug product (reviewed by Julia Pinto, Ph.D. and Ted Carver, Ph.D.).

The drug product is formulated as a 12-hour extended release suspension indicated for the treatment of allergic rhinitis. The immediate release Carbinoxamine Maleate oral solution (4mg/5ml) marketed by Mikart, is the innovator product and is the reference listed drug (RLD) for the development of the ER product. The formulation is in a concentration of 4mg/5ml and uses the polistirex drug delivery technology that involves the (b) (4) . In the gastrointestinal tract, counter ions penetrate the complex and displace the drug from (b) (4), so that it slowly diffuses from the complex and is then freely absorbed over a longer period of time. The manufacturing process is a (b) (4)

(b) (4)

(b) (4)

. The drug product is packaged in bottles and to be stored under recommended conditions of 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months. The "Karbinal ER" tradename, submitted to the NDA, is under review with DDMAC and acceptability of the name is pending.

B. Description of How the drug is intended to be used:

Carbinoxamine maleate ER 4mg/5ml oral suspension is an extended release oral suspension of carbinoxamine maleate, an anti-histamine agent indicated for the treatment of allergic rhinitis.

C. Basis for Approvability Recommendation

Insufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. Several deficiencies were observed, in the manufacture and control of the drug product. Further, an overall recommendation is pending from the office of compliance, for the drug substance and drug product manufacturing sites wherein the DP site is recommended as a "withhold". Therefore this NDA is recommended as approvable pending the resolution of the deficiencies listed at the end of this review and a satisfactory recommendation from Office of Compliance (OC).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.; Ted Carver, Ph.D.; Donald Klein, Ph.D.
Pharmaceutical Assessment Leader: Alan C. Schroeder, Ph.D.
Project Manager: Miranda Raggio, BA, BSN, MA
Branch Chief: Prasad Peri, Ph.D.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA C PINTO
09/07/2011

PRASAD PERI
09/07/2011
I concur

OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment
Date: January 21, 2010

NDA: 22-556
Product Name: Carbinoxamine Extended Release Oral Suspension
Applicant: Tris Pharma Inc.
Stamp Date: 12/08/2010
PDUFA Date: 10/08/2011
ONDQA 5 month date: 5/08/2011
Proposed Proprietary Name: None proposed yet
Established Name: Carbinoxamine Extended Release Oral Suspension
Maximum daily dose (adults): 32 mg
Dosage form and strength: Extended Release Oral Suspension (4 mg/5 mL)
Route of Administration: Oral
Indications: Seasonal and perennial allergic rhinitis (and a number of other indications)
CMC Lead (acting): Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA
Filability recommendation: Fileable from a CMC standpoint
Review team recommendation: Single primary reviewer (Theodore Carver, Ph.D.)
Time goals:

- Initial Quality Assessment in DFS: February 8, 2011
- Filing decision "Day 45": January 22, 2011 (Filing meeting January 19, 2011)
- Filing review issues "Day 74": February 18, 2011 (74-day letter)
- **Chemistry Review (DR/IR) letter:** May 9, 2011
- Mid-cycle meeting "Month 5": May 8, 2011
- Wrap Up Meeting: August 29, 2011
- **Final Chemistry Review "Month 8" in DFS: August 8, 2011**
- PDUFA: October 8, 2011

CONSULTS/ CMC RELATED REVIEWS	**COMMENT**
Biopharm	Requested (since this is an extended release product)
CDRH	Not required
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 1/20/2010
DMETS	Labeling consult request will be sent as part of DPARP's request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.
Microbiology	Recommend request, at least informally.
Pharm/Tox	DS and DP impurities/degradants/leachables to be evaluated for safety if necessary. The current drug product specification has no specified impurities, and unspecified impurities are limited individually to a maximum of (b) (4) to the ICH Q3B qualification threshold.

Note: tables and chemical structures in this review are obtained from the applicant (NDA).

The IND for this drug product (IND 102091) includes the proposed (b) (4) drug product (b) (4)

(b) (4)

Meeting minutes are provided for an IND 102091 meeting between representatives of the sponsor and of the FDA, held on May 15, 2008.

DMFs: letters of authorization are provided for the following DMFs. This information is from the applicant.
(Reviewer should check for LOA for DMF (b) (4) which seems to be missing.)

(b) (4)

The drug substance DMF (# (b) (4) was first submitted in (b) (4) and it has not yet been reviewed.

Drug substance

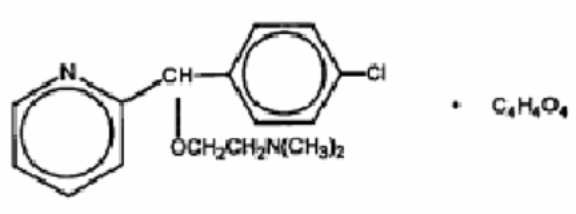
Information from the applicant:

Nomenclature:

International Non-proprietary Name (INN): Carbinoxamine Maleate USP

Chemical Name: 2-[(4-chlorophenyl)-2-pyridinyl-methoxy)-N,N-dimeythylethanamine (Z)-2-butenedioate (1:1)

Molecular Structure:



Molecular Formula: $C_{16}H_{19}ClN_2O \cdot C_4H_4O_4$

Molecular Weight: 406.86

Drug substance manufacturer: (b) (4) (b) (4)
The drug substance is (b) (4) with the Polistirex (b) (4) therefore physical properties of the drug substance are not critical.

Drug substance specifications from the applicant:

Tests	Specifications
Description	White, crystalline powder.
Identification	
A. Infrared Absorption	Sample exhibits maxima only at the same wavelengths as that of a similar preparation of the corresponding standard.
B. Ultraviolet Absorption	Absorptivities at 260 nm calculated on the dried basis, do not differ by more than 3.0%.
Melting range	Between 116° and 121° C, determined after drying
pH	Between 4.6 and 5.1
Loss on Drying	Not more than 0.5%
Residue on ignition	Not more than 0.1%
Assay	98.0 to 102.0% calculated on the dried basis.
Residual Solvents	(b) (4) (b) (4)
Impurities	Specified Impurities (b) (4) NMT (b) (4) NMT NMT NMT Unspecified Impurity: NMT Total Impurities[4]: NMT

Tests	Specifications
Description	White, crystalline powder.
Identification	
A. Infrared Absorption	Sample exhibits maxima only at the same wavelengths as that

Notes regarding drug substance specifications: residual solvents are based on solvents used in the drug substance manufacturing process. Upper limits for the specified residual solvents are below the limits in the ICH Q3C guidance. Impurity specifications are said to be based on acceptance criteria in the manufacturer's COA. The manufacturer's COA indicates an (b) (4) retest period for the drug substance. The applicant has provided analytical methods and validation data for the following drug substance methods: assay, residual solvents, impurities. These methods were transferred from the drug substance manufacturer. Other methods are indicated to be compendial (except for the description).

The structures of the specified impurities are reproduced below from the applicant. They (as well as the unspecified impurities) are controlled below the qualification threshold for this drug substance, as indicated in the ICH Q3A(R) guidance for drug substances. The specified impurities do not contain structural alerts.

Specified Impurities

Drug Product:

Drug product composition (compared in the second table below with limits in FDA's "Inactive Ingredient Guide" (IIG)):

Ingredients	Quantity (mg per 5 mL)
Sodium Polystyrene Sulfonate (b) (4) [1]	(b) (4)
Povidone USP (b) (4)	
Triacetin USP	
Polyvinyl Acetate (b) (4)	
(b) (4)	
Purified Water USP	
Polysorbate 80 NF ((b) (4)	
Sodium Metabisulfite NF (b) (4)	
Carbinoxamine Maleate USP	
Glycerin USP	
Methylparaben NF	
Propylparaben NF	
Xanthan Gum NF ((b) (4)	
Anhydrous Citric Acid USP	
High Fructose Corn Syrup (b) (4)	
Sucrose NF	
(b) (4) (Food Starch – Modified)	
Strawberry Banana Flavor (b) (4)	
(b) (4): (b) (4)	
(b) (4): (b) (4),	
(b) (4)- (b) (4)	

[1] Sodium Polystyrene Sulfonate USP (b) (4) is (b) (4), then assigned (b) (4)
[2] Amount represents (b) (4)
[3] Amount represents

Ingredients	Quantity (w/v%)	Amount allowed per IIG (%)
Sodium Polystyrene Sulfonate [1]	[b) (4)]	[b) (4)]
Povidone USP	[b) (4)]	
Triacetin USP		
Polyvinyl Acetate	[b) (4)]	
[b) (4)]		
Purified Water USP		
Polysorbate 80 NF	[b) (4)]	
Sodium Metabisulfite NF	[b) (4)]	
Glycerin USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF	[b) (4)]	
Anhydrous Citric Acid USP		
High Fructose Corn Syrup	[b) (4)]	
Sucrose NF		
[b) (4)] Food Starch – Modified)		
Strawberry Banana Flavor [b) (4)] (includes):		
[b) (4)]		

[1] Sodium Polystyrene Sulfonate USP [b) (4)]
[2] Above amount allowed as per IIG database. A qualification report is available in Module 4.2.3.7.7.
[3] Amount represents [b) (4)]
[4] Amount represents
[5] Ingredient is not found in IIG database. Material is GRAS as per manufacturer's statement.

It may be noted that the following excipients: polyvinyl acetate [b) (4)], high fructose corn syrup, [b) (4)] (food starch) and the strawberry banana flavor are not compendial items. The reviewer also needs to evaluate these excipients for their quality and for their qualification status (at the proposed levels) relative to the IIG, if the IIG contains data on identical excipients. A wider search of levels of the excipients in approved NDAs may also be conducted. It should be determined from this search whether the excipients or their constituents may need pharm/tox assessment at their proposed levels.

There are supporting DMFs for the following excipients: povidone, sodium polystyrene sulfonate, polyvinyl acetate [b) (4)] and strawberry banana flavor which need to be checked to see if they need to be reviewed.

Specifications for the excipients are compendial. Where no compendial specifications exist, the applicant has developed their own.

Drug Product Specifications:

Tests	Specifications
	(b) (4)

The first identification specification (drug product) mentions the " (b) (4) *" and this should be corrected. The sponsor should ensure that these are the correct drug product specifications*. Batch release data are provided in certificates of analysis; the data appear to be generally similar across batches, with some variability in dissolution ranges. Information is provided about reference standards.

The applicant has evaluated residual solvents for the drug substance and for each excipient, and has provided a table showing the maximum solvent present in each component and a table comparing the total daily exposure for each solvent to the maximum permitted daily exposure (PDE) per USP <467>. *It should be noted that the maximum exposure for* (b) (4) *(impurity in* (b) (4) *) in the drug product is close to the maximum PDE, and this should be brought to the attention of the pharm/tox reviewer.*

Preservative specifications are based on the results of the preservative effectiveness test results. These results have not been reviewed here, and it isn't certain whether they were submitted to the NDA (*the applicant should clarify this*).

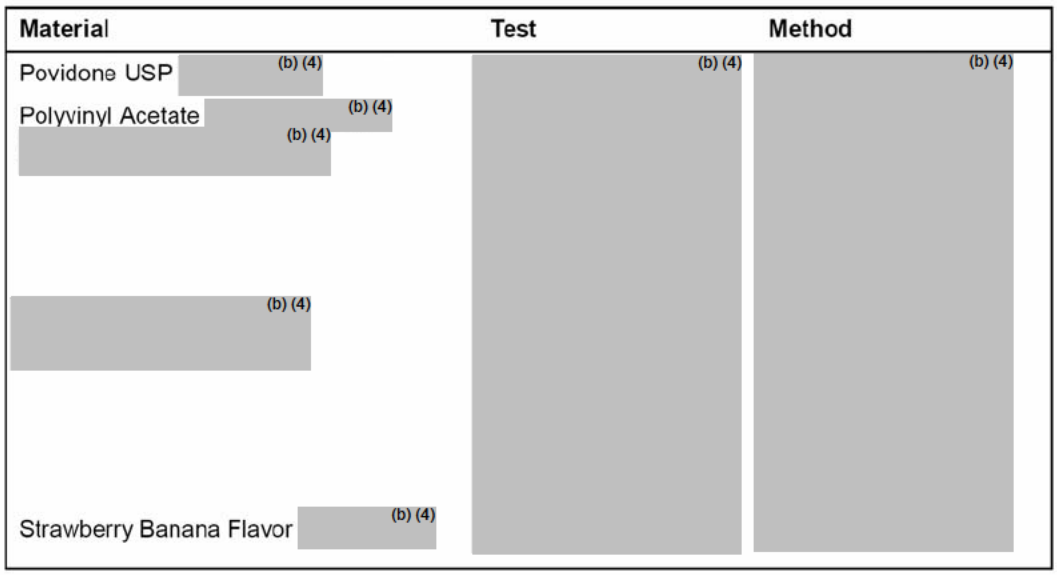
A pharmaceutical development report is provided for the drug product (40 pages), which highlights "the formulation development, the release profile and chemical stability of the proposed formula, scale-up development and the proposed manufacturing process..." Background: The drug product is an oral antihistamine with a 15-20% sedation rate. The proposed Carbinoxamine Maleate ER Oral Suspension is a 12-hour ER formulation. The reference product is Carbinoxamine Maleate Oral Solution (4 mg/5 mL). The applicant [redacted] A unique process of [redacted] This provided the basis for selection of the prototype formula. The critical process parameters were determined during scale up development using pilot scale equipment. The remaining ingredients include the following: [redacted], sodium metabisulfite [redacted], polysorbate 80 [redacted] to disperse the particles, citric acid [redacted], sucrose and high fructose corn syrup ([redacted]), [redacted] and xanthan gum [redacted] the parabens ([redacted]), and strawberry banana flavor.

The drug product is manufactured and tested by Tris Pharma Inc. (Monmouth Junction, NJ). Drug product testing (for microbial limits) is also performed by [redacted] ([redacted] The batch formulas and proposed production batch scales are provided for the sodium polystyrene sulfonate [redacted] The test batch scale of the final drug product was [redacted] kg and the intended production batch scale of the final drug product is [redacted] kg, therefore a [redacted] fold scale up is proposed. Descriptions of the manufacturing process, process controls and are provided both in bullet format and as process flow diagrams.

The "Regional Information" section of the NDA provides a variety of information including, for example, executed batch records for the various processes, certificates of analysis for the excipients, and method validation assay data for drug product methods

for assay, dissolution, impurities and preservatives. See also section P.5.3 for validation data.

Analytical methods for excipients are compendial, except for the following identified non-compendial methods:



]

Validation reports and data are provided for chromatographic non-compendial excipient methods (e.g., (b) (4)) following a validation approach which the applicant claims is in accord with ICH Q2A and Q2B guidances.

Container Closure System:

Item	Description	Quantity per Unit	Comments
(b) (4)			

See DMFs for additional container closure component information (the list is provided earlier in this review). The NDA provides schematic container closure component drawings, certificates of analysis and other component information.

Stability:

"The stability test methods are description, color test, pH, microbial limits, preservative, assay, dissolution, and impurity for the drug product (b) (4) ER Oral Suspension, eq. to 4 mg carbinoxamine maleate per 5 mL. The test methods used for the drug product release are stability-indicating, so the same methods are utilized for stability. All stability specification limits for drug product are the same for the drug product release."

"Accelerated studies were conducted at 40 ± 2°C and 75 ± 5% relative humidity with samples analyzed at 1, 2, 3, and 6 months, intermediate studies at 30 ± 2°C and 65 ± 5% relative humidity at 3, 6, 9, and 12 months, and room temperature studies at 25 ± 2°C and 60 ± 5% relative humidity for two and a half (2½) years with sampling intervals at 3, 6, 9, 12, 18, 24, and 30 months." Note that the latter room temperature study is underway, only completed to the 18 month time point in this NDA.

"Comparison of 6-month accelerated stability data (40°C/75%RH), 6-month intermediate stability data (30°C/65%RH) and 6-month room temperature stability data (25°C/60%RH) for the test batches, TB-024A, TB-026A, and TB-027A, have been provided for the drug product in the proposed (b) (4) Container Closure system." The applicant claims that the resultant stability data (for accelerated conditions) are within the proposed stability specifications for the proposed expiration dating period. This appears to be true for the three batch summary stability data provided (0 and 6 months data only) at all storage conditions, with the exception that there were at least a few dissolution outliers in the individual data. A 24 month expiration dating period is proposed. Stability data are provided through 18 months at 25°/60%RH for three drug product lots (batch scale is (b) (4) kg, which is equal to (b) (4)% of the proposed production batch). Accelerated stability data (40 deg./75%RH) are provided through 6 months, and intermediate stability data (30 deg./65%RH) through 12 months. The stability storage position of the drug product is horizontal in the stability studies. *The reviewer needs to determine if this single storage position is adequate.*

Stability data for impurities (degradants)are at very low levels. The analytical methods (and validations of these methods) should be evaluated to make sure that all potential degradants are capable of being detected and quantified with the proposed method.

Post-Approval Stability Commitment: see Section 3.2.P.8.2. The three point stability commitment is provided: i.e., the applicant will conduct the stability studies at room temperature, they will report the results of the studies, and any production batch which is outside the approved drug product specifications will be investigated. The language used in this commitment is not completely standard relative to batches which fail stability specifications and should be evaluated. Justification is needed for the continuing

Component	Manufacturer	DMF No.
Sodium Polystyrene Sulfonate USP (b) (4)	(b) (4)	(b) (4)
Povidone USP (b) (4)		(b) (4)
Polyvinyl Acetate Dispersion (b) (4)		(b) (4)
Carbinoxamine Maleate USP		(b) (4)
Strawberry Banana Flavor (b) (4)		(b) (4)
Container, (b) (4) Container (b) (4)		(b) (4) (b) (4)
Closure (b) (4) Closure, (b) (4) (b) (4)		(b) (4) (b) (4) (b) (4) (b) (4)
(b) (4)		(b) (4) (b) (4) NA

marketing of any batch of drug product which fails a specification, and that issue should be discussed with the FDA review division. Other potential issues include the following: the applicant proposes to (b) (4)

Filing Check List (reproduced from filing meeting slides):

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract	x		

	facilities and test laboratories) identified with full street addresses and CFNs?			
5	Is a statement provided that all facilities are ready for GMP inspection?	x		FDA form 356h indicates that all sites are ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	x		Section 1.12.14 claims a categorical exclusion.
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Have stability data and analysis been provided to support the requested expiration date?	x		Stability data have been provided through 18 months; requested expiration dating period (b) (4)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	partially		The stability data are not in the recommended format but the data are concise enough for review. It is not clear whether CQAs and CPPs are listed, but quality attributes and process parameters are discussed. The requested alcohol dose dumping study was performed on the drug product: NDA Module 5.3.1.3. (see request in minutes of 5/15/08 pIND 102091 tcon) . These are review issues rather than filing issues.
11	Have draft container labels been provided?	x		carton labels are not provided but see item #12 below
12	Has the draft package insert been provided?	x		labeling indicates that drug product is to be dispensed in tight, light-resistant container with child-resistant closure. The drug product container is made of (b) (4), and no carton is indicated.
13	Has an investigational formulations section been provided?	x		Section P.2.
14	Is there a Methods Validation package?	partial		Some of this information is referenced in Sections

				3.2.P.5.3 and 3.2.S.4.3. A tabular listing of samples to be submitted is not provided, nor are material safety data sheets provided for substances to be supplied to the laboratories. This information could be provided with samples.

Certain review issues which were noted are listed below for consideration by the reviewer:

The reviewer should see whether the applicant has provided information pertaining to drug product characterization (e.g., resuspendability), and should consider whether a drug product specification for resuspendability is needed.

Check for an LOA for DMF (b) (4) which seems to be missing (for the (b) (4)), if the DMF is determined to be needed for review.

Evaluate the non-compendial excipients of the formulation for their quality and for their qualification status (at the proposed levels) – see details earlier in this review.

It should be noted that the maximum exposure for (b) (4) *(impurity in* (b) (4) *in the drug product is close to the maximum PDE, and this was indicated at the filing meeting.*

The stability storage position of the drug product is horizontal in the stability studies. *Determine if this single storage position is adequate.*

The word "Polistirex" does not appear in the labeled name. The reviewer needs to determine whether this is acceptable or not.

The following comments pertain to the post-approval stability commitment. The language used in this commitment is not completely standard relative to batches which fail stability specifications and should be evaluated. Justification is needed for the continuing marketing of any batch of drug product which fails a specification, and that issue should be discussed with the FDA review division. Other potential issues include the following: the applicant proposes to (b) (4)

(b) (4)

IND Information relevant to CMC review: see pIND tcon minutes (tcon date: 5/15/2008)

Comments for the Applicant:
The first identification specification (drug product) mentions the "(b) (4) and this should be corrected. Ensure that these are the correct drug product specifications.

Provide a reference to preservative effectiveness testing and data in the NDA, or provide that information.

Since the drug formulation contains a significant level of glycerin which may be considered as a (b) (4), as well as significant levels of other excipients (other that (b) (4)), provide data and controls for container closure component extractables (e.g. using a range of solvent polarities and multiple extraction conditions), and for leachables that are found in the drug product formulation over its shelf life. Alternatively, provide a data based justification for a lack of controls for extractables and leachables. For any extractables and leachables which were identified, provide a safety assessment of such extractables and leachables.

Recommendation: The NDA is fileable from a CMC perspective.

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: ____x___Yes; _____No Review date:
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No__x____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes No
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble **(**e.g., gold nanoparticle**)** in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

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/s/

ALAN C SCHROEDER
01/21/2011
CMC Recommendation: fileable

PRASAD PERI
01/21/2011
I concur