CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-604

CHEMISTRY REVIEW(S)

NDA 21-604

Children's ElixSure™ Ibuprofen Oral Suspension

Taro Pharmaceuticals USA Inc.

Vispi P. Bhavnagri
HFD 550
HFD 560

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-604

2. REVIEW #: 1

3. REVIEW DATE: 8-Oct-2002

4. REVIEWER: Vispi P. Bhavnagri

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62,832	Aug-2-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Dec-2002
Minor Chem. Amendment (BC)	24-Jan-2003
Minor Chem. Amendment (BC)	31-Jan-2003
Minor Chem. Amendment (BC)	7-Mar-2003
Minor Chem. Amendment (BC)	20-Jun-2003
Minor Chem. Amendment (BC)	27-Jun-2003
Minor Chem. Amendment (BC)	22-Jul-2003
Minor Chem. Amendment (BC)	23-Sep-2003
Multidisciplinary Amendment (BZ)	30-Sep-2003
Minor Chem. Amendment (BC)	1-Oct-2003
Minor Chem. Amendment (BC)	8-Oct-2003
Minor Chem. Amendment (BC)	23-Oct-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Taro Pharmaceutical USA, Inc.

Address: Five Skyline Drive, Hawthorne, NY 10532

Chemistry Review Data Sheet

Representative: Kalpana Rao, Vice President, Regulatory Affairs

Telephone: 914-345-9001 ext. 298

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name : Children's ElixSure™ Ibuprofen Oral Suspension
b) Non-Proprietary Name (USAN): Ibuprofen
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505 (b)(2)

10. PHARMACOL. CATEGORY:

Analgesic and antipyretic

11. DOSAGE FORM:

Suspension

12. STRENGTH/POTENCY:

100 mg/5 mL

13. ROUTE OF ADMINISTRATION:

Oral

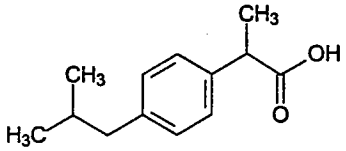
14. Rx/OTC DISPENSED: ___Rx _X__OTC

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:

Benzeneacetic acid, a-methyl-4-(2-methylpropyl), (±)
(±)- p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid.



$C_{13}H_{18}O_2$
206.28

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	4/25/03	
	II			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4	N/A		
[redacted]	III	[redacted]	[redacted]	4	N/A		

[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	62,832	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Acceptable	9/29/03	S. Adams
Pharm/Tox	Approval	8/19/03	Conrad Chen
Biopharm	Acceptable	10/25/03	Lei Zhang
LNC	Acceptable	10/24/03	Linda Kim-Jung
Methods Validation	Will be sent to FDA Lab		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

The Chemistry Review for NDA 21-604

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved from a CMC standpoint.

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

None.

II. Summary of Chemistry Assessments

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

Drug Substance:

Ibuprofen is manufactured and supplied by [redacted] The manufacture and control of the drug substance were referenced to DMF [redacted] The DMF has been recently reviewed and found to be adequate. Test and acceptance criteria meet and in some cases exceeded the requirements of the USP.

Drug Product:

The drug product is a berry flavored pediatric ibuprofen suspension containing 100 mg of ibuprofen per 5 mL of the suspension. Though almost all the components of the formulation are USP or NF articles, the formulation is unique in that it is thixotropic, thus it flows on to the spoon when the bottle is squeezed but gels on the spoon so that it can be administered to children without spilling. The manufacture of the drug product does not require many controls. However, the control of the pH between 4.9 and 5.7 pH units is critical to the flow properties of the drug product.

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

The drug product is intended for oral administration. Five mL of the suspension contains 100 mg of ibuprofen. The dose is 5 mL to 15 mL three to four times a day. It is administered with a special plastic spoon that has 5 and 2.5 mL markings on it (part of the container closure system).

The company has asked for a 24 month expiration period based on 24 months of room temperature stability data (25° C/60% RH). An expiration period of 24 months can be granted based on the stability results submitted. The company eventually intends to have a shelf life of 5 years for this product.

C. Basis for Approvability or Not-Approval Recommendation

Ibuprofen is a USP article and has been in use for a long time. The acceptance criteria for the drug substance used in this drug product has additional tests and acceptance criteria over and above those in the USP. The acceptance criteria for some of the USP tests are also more stringent.

The only critical control during the manufacturing of the dosage form is pH, which must be within certain limits if the drug product is to have the desired flow properties. The stability of the dosage form over 24 months does not show any instability trends that would be cause for alarm. The applicant was asked to and has complied with tightening the dissolution and other acceptance criteria thereby ensuring consistency in the quality, strength and potency of the drug product.

There is one drug substance and one drug product manufacturing facility and a number of contract labs performing analytical procedures for the various components of the drug product. All of these facilities were found to be acceptable. An overall "Acceptable" recommendation was issued by Compliance on 9/29/03.

The company has asked for a categorical exclusion under the provisions of 21 CFR 25.3(a), which is acceptable.

III. Administrative

A. Reviewer's Signature:

N/A

B. Endorsement Block:

N/A

C. CC Block:

N/A

40 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1 of 1

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

/s/

Vispi Bhavnagri
10/28/03 03:07:31 PM
CHEMIST

John Smith
10/28/03 03:14:10 PM
CHEMIST