CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

6-488/S019

Trade Name: Xylocaine

Generic Name: lidocaine hydrochloride

Sponsor: Astra Pharmaceutical Products, Inc.

Approval Date: 02/27/1979

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-488/S019

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	✓
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-488/S019

APPROVAL LETTER

NDA 6488/S-019

Astra Pharmaceutical Products, Inc.
Attention: David W. Blois, Ph.D.
Neponset Street
Worcester, MA 01606

FEB 23 1979

Gentlemen:

We acknowledge the receipt on February 2, 1979, of your communication dated January 30, 1979, regarding your supplemental new drug application of October 13, 1978, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xylocaine (lidocaine hydrochloride) Solution.

The supplemental application provides for the alternate use of The [redacted] (b)(4) [redacted] (b)(4) rubber closure as a packaging component for the single and multiple dose vials of Xylocaine Solution.

We have completed the review of this supplemental application as amended and it is approved. Our letter of December 4, 1972, detailed the conditions relating to the approval of this application.

Sincerely yours,

James P. Mann, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

APPROVAL

cc: NDA 6488/S-019
BOS-DO (HFR-1100)
HFD-160
HFD-616
R/D SKoch(HFD-160)2/7/79
R/D Init by RAJerussi 2/13/79 and
JPMann 2/15/79
Final typed nm 2/23/79
Doc.Rm. 160.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-488/S019

CHEMISTRY REVIEW(S)

CHEMIST - REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-160

2. NDA NUMBER: 6488

3. NAME AND ADDRESS OF APPLICANT (City and State)
Astra Pharmaceutical Products Inc
Worcester, Mass 01606

4. AF NUMBER: 31-390

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-019	10-13-78

6. NAME OF DRUG: Xylocaine HCl Inj.

7. NONPROPRIETARY NAME: lidocaine HCl

8. SUPPLEMENT(S) PROVIDES FOR:
(b) (4) formulation as additional source of supply for SDV & MDV Xylocaine products cleaning; application presently provides for (b) (4)

9. AMENDMENTS AND OTHER (Reports, etc.) DATES
1-30-79 S/A.

10. PHARMACOLOGICAL CATEGORY: anesthetic

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)
(b) (4) (DMF - Astra), DMF (b) (4)

13. DOSAGE FORM (S): sterile soln

14. POTENCY (Iea): 0.5 → 2.0%

15. CHEMICAL NAME AND STRUCTURE
24 mo exp. date solutions c epi.
48 mo exp. date plain solns.

16. RECORDS AND REPORTS
CURRENT: ☐ YES ☐ NO
REVIEWED: ☐ YES ☐ NO

17. COMMENTS (b) (4)

cc: NDA-6488, HFD-160, D
R/D SKoch 2/7/79
Init RJerussi 2/13/79
Xeroxed 2/23/79; Doc. Rm. 160

Jan 30 S/A provides info on issues raised in 1-16-79 [illegible]
Astra release spec on $Na_2S_2O_5$ is 0.50 mg/ml. the stability agreement for (b) (4); (b) (4) lots of each of the following:
production lots using

50 ml MDV - 0.5% plain soln
50 ml MDV 0.5% with epi 1:200,000
20 ml MDV 2% plain
20 ml MDV 2% with epi 1:160,000

Firm places (b) (4) of all production lots (minimum (b) (4) of dosage form on stability each year.
Data will be submitted q 6 mos first year, annually thereafter to exp. date. the remaining portion of stability commitment received. See 1/16/79 and 1/19/79 telephone conversation MEMO's. Data on laboratory batches to be continued to exp. date, data reported annually.

2/13/79

18. CONCLUSIONS AND RECOMMENDATIONS

→ Recommend approval S-019.

It appears the methods & specifications developed by Astra to control rubber compositional variation and ethylene degradation will survive Agency review, although the HFD-232 statistical review requested by HFD-160 on 10/23/78 is not yet in hand. The Applicants reports on this subject form the basis for the (b) (4) content stopper spec in this supplemental application.

Reg

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
S. KOCH	Sarla Koch	2-7-79

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-488/S019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMO RECORD | AVOID ERRORS PUT IT IN WRITING | DATE January 19, 1979

FROM: Telephone conversation initiated by DR. David Blois, Astra Pharmaceutical Products, Inc. | OFFICE | DIVISION

TO: S. KOCH HFD-160

SUBJECT: NDA 6488/S-019 (10-13-78)

SUMMARY

See telephone MEMO dated 1-16-79.
Dr. Blois called back to offer their proposal on dosage forms of Xylocaine MDV's and ~~SDV's to be~~ placed on stability study [redacted] (b) (4) Their proposal:

[redacted] (b) (4) production lots of 50 ml MDV 0.5% plain
50 ml MDV 0.5% epi 1:200,000
20 ml MDV 2.% plain
20 ml MDV 2.% epi 1:100,000

for a total of [redacted] (b) (4) production lots. The normal routine at Astra, according to David, is to place [redacted] (b) (4) of each dosage form per year on shelf study (if [redacted] (b) (4) lots, put [redacted] (b) (4) on stability) down to a minimum of [redacted] (b) (4) lot for each dosage form; these samples therefore are taken in addition to the [redacted] (b) (4) lots cited above. Astra's reasoning on the 4 dosage forms selected above is to place both the highest surface-to-volume ratio (20 ml) and lowest surface-to-volume ratio (50 ml), 2% and 0.5% concn's respectively, on stability. [The components for MDV & SDV are identical. Stopper which may be used limited to [redacted] (b) (4) and [redacted] (b) (4) are approved for use)

1/24/79
Spoke with Dr. Blois today and indicated to him that preliminary discussions with Dr. Jenssi led me to believe the proposed stability program will be acceptable using the four dosage forms outlined above along with the data accumulated from [redacted] (b) (4) of each of the other dosage

SIGNATURE | DOCUMENT NUMBER

FORM FD 2034 (6/76)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE January 19, 1979
FROM: DR. BLOIS		OFFICE
TO: S. KOCH		DIVISION P.272
SUBJECT: NDA 6488/S-019		

SUMMARY

forms per year.
Astra will put together the injunctions requested and submit as a supplement amendment in a day or two.

Stanley Koch 1/25/79

RaJ 2/13/79

FEB 2 9 1979

cc: NDA 6488/S-019
HFD-160(2)
R/d SKoch(HFD-160)1/25/79
Init RAJerussi 2/13/79
Xeroxed 2/23/79
Doc Rm. 160

SIGNATURE	DOCUMENT NUMBER

FORM FD 2034 (6/76)

MEMO RECORD | AVOID ERRORS PUT IT IN WRITING | DATE January 16, 1979

FROM: telephone conversation initiated by S. KOCH HFD-160 | OFFICE

TO: David BLOIS, Drug Regulatory Affairs, Astra Pharmaceutical Product | DIVISION

SUBJECT: NDA 6488/S-019 (10-13-78)

SUMMARY

I called to request additional information on this supplemental application:

(1) NDA release specifications on sodium metabisulfite in solutions with epinephrine; shelf-life specs, in-house or otherwise, on $Na_2S_2O_5$ levels, and Astra opinion on minimum acceptable amount necessary to accomplish purpose for including in formulation.

(2) reasons for request of yet another stopper material. David says firm may wish [redacted] (b) (4) as a manufacturer, and [redacted] (b) (4) cannot meet demand.

(3) the number of initial production lots to be placed on stability, and those combinations of vial size & formulation to be represented. I suggested elimination of selected dosage forms if bracketed by similar concentration of lidocaine within a given vial size; i.e., 1% plain and with epi solutions in MDV, perhaps 30ml 1% plain in SDV, 50ml 0.5% plain in [redacted] (b) (4) SDV included in study. Astra will get back by telephone with a proposed listing of dosage forms to be placed on stability. The stability commitment should include following: "accumulated data will be reported every 6 months for the first year, annually thereafter to the expiration date, at a minimum, and that laboratory kit studies continue to expiration dating period with data submitted as above.

(4) evidence that [redacted] (b) (4) are approved across the board, as indicated on p. 2 of submission.

This info should be gathered for submission in 2 weeks, according to Dr. Blois.

FEB 27 1979

cc: NDA 6488/S-019
HFD-160(2)
R/d SKoch 1/16/79
Init RAJ 2/13/79

Raj 2/13/79

SIGNATURE Stanley Koch 1/16/79

DOCUMENT NUMBER Doc.Rm. 160
Xeroxed 2/23/79.

FORM FD 2034 (6/76)

Memorandum of Telephone Conversation

December 13, 1978

Between: Mr. David Boyce
Director of Regulatory Affairs
Astra Pharmaceuticals

and

Michael Schapira, Ph.D.
Chao W. Chen, Ph.D.
Statistical Evaluation Branch, HFD-232
Division of Biometrics

Subject: NDA 6488, Degredation of Epinephrine in Xylocane

As a follow-up to our conversation on November 16, Mr. Boyce called us. We asked Mr. Boyce some questions and he answered them. The substance of the questions and answers follow:

1. How were the samples taken? All lots were beyond the expiration date (more than 27 months). They were chosen on the basis of their low epinephrine values, (one or more vials were sampled per lot) or if the closure used was of the same material as one which had a confirmed low value.

2. Explain why in the data used in the statistical analysis only extreme values occur with respect to [redacted] (b)(4) concentrations. They have submitted data with intermediate values to HFD-160. (see also question 8) But these data were not included in the statistical analysis currently under our review.

3. Explain why the upper confidence limit was used to determine maximal allowable [redacted] (b)(4) concentration of the stoppers. This was the workable level at which [redacted] (b)(4) could supply the stoppers. It was a practical decision, not a statistical one. Moreover, the lots were all tested at 27 months. We pointed out that the effect of using only 27-month data without using data at any other time points would be difficult to assess exactly.

4. Have the lots with low values been removed from the market? Yes, all such lots have been removed.

5. What is the status of the asterisked lots in Table I where the epinephrine concentrations are between [redacted] (b)(4) so all these lots are within specification limits.

6. Is the statistical analysis done this time essentially the same as last time and done on the same data? It was essentially the same with some corrections on the formulae. The same data was used.

7. The two lower limits calculated by the sponsor were different (b)(4) Which lower limit is the company claiming is correct? (b)(4)- is what they stand by. They also say that (b)(4) is the minimum allowable (b)(4) concentration.

8. We asked them to use all available data points including the extremes and points in between and do a regression analysis, calculate a one-sided lower confidence limit, tabulate all the data used in a complete data display, and send the material to us in 4 weeks. Mr. Boyce said that the 33 points used in their statistical analysis were all the points at 27 months. There were no more values at 27 months. He said (b)(4) values are constant over time, but the epinephrine values are time dependent. There do exist intermediate data points as far as the (b)(4) values are concerned at 27 months, but no epinephrine values at 27 months. They analyzed the complete data set at 27 months. We asked if they had any 24-month data. He said he'd check. We asked if they could give us the computer cards so we could do an analysis faster. He said the information on data points is in HFD-160 and that the information on the cards may be more confusing since it would include data points before 24 months and perhaps give a false impression of very good results being that the epinephrine values decrease over time. They were concerned about the times at which the batches were tested.

Mr. Boyce said they do have a regular stability testing program. He said the solution to the problem is to establish controls on the currently-used rubber. (b)(4)

Michael Schapira, Ph.D.
Mathematical Statistician

Chao W. Chen, Ph.D.
Mathematical Statistician

DEC 13 1978

cc:
Orig. NDA 6488
HFD-160
HFD-160/Stanley Koch
HFD-232/Dr. Dubey
HFD-232/Dr. Chen
HFD-232/Dr. Schapira
Chron.
MSchapira/CChen/ed/rab/12/13/78

Memorandum of Telephone Conversation

December 13, 1978

Between: Mr. David Boyce
Director of Regulatory Affairs
Astra Pharmaceuticals

and

Michael Schapira, Ph.D.
Statistical Evaluation Branch, HFD-232
Division of Biometrics

Subject: NDA 6488, Degredation of Epinephrine in Xylocane

We called Mr. Boyce. Mr. Boyce explained that they have alternative rubber formulations - (2 for the vials). [redacted] (b)(4) In the literature, [redacted] (b)(4) does have an effect on the degredation of epinephrine [redacted] (b)(4). Everything indicates [redacted] (b)(4) to be responsible. They tested with other metals and are satisfied it is the [redacted] (b)(4) By controlling the rubber used, they can get adequate stability - they reconstructed the problem.

Michael Schapira, Ph.D.
Mathematical Statistician

cc:
Orig. NDA #6488
HFD-160
HFD-160/Mr. Stanley Koch
HFD-232/Dr. Dubey
HFD-232/Dr. Chen
HFD-232/Dr. Schapira
Chron.
MSchapira/ed/rab/12/13/78

NDA 6-488

October 25, 1978
9:00 - 11:30

MEMORANDUM OF MEETING

BETWEEN: Astra Pharmaceuticals
Gerard M. Boyce
David W. Blois, Ph. D.
Michael D. Young, M. D., Ph. D.
Thomas O. Henteleff
Sigmund M. Warasvckewicz

West Company
Frank M. Keim
F. Wm. Boglie

AND: FDA
Dr. Jerussi, Acting Director
Stanley Koch, Acting Supervisory Chemist
Walter Brown, Compliance
John Singer, Consumer Safety Officer

SUBJECT: NDA 6-488 Xylocaine 2% Solutions Rubber stopper problems

The Astra presentation was initiated by David Blois, Drug Regulatory Affairs. Dr. Blois explained the reason for their visit, and indicated their effort was largely for the benefit of the Division of Surgical Dental Drug Products; i. e., to answer certain questions raised by our May 17, 1978 Information Request letter, and to bring Division representatives up-to-date on the research-and-correct-program accomplishments at Astra on the epinephrine subpotency problem as well as the occurrence of stopper particulation. He indicated that over (b)(4) lots have been withdrawn or recalled from the market place over the past 18 months due to these apparent stopper or I-cap problems.

Mr. Gerard Boyce, Director of Pharmaceutical Development, followed with a review of data accumulated and conclusions derived from the epinephrine subpotency studies on vial products, Astra Report 4022W4. This was discussed from the standpoint of:

1. Identification of cause of subpotency via work on assay procedure, vial, solution analysis (Al^{+++}, Zn^{++}, Cu^{++}, etc.), rubber closure analysis

2. verification of results via simulation in laboratory

3. preventery recurrence

    a. selection of a maximum (b)(4) level in closures

    b. vial closure sampling plan - sample in a sequential manner

to cover all rubber mixes in a given closure lot. (b) (4) [redacted]

The bulk of material Mr. Boyce covered has been submitted to the NDA 6488 file.

Dr. Sigmund M. Warasvckewicz followed with a similar presentation on the dental cartridge cap liner problem, a review of Astra report 4022W6. A course & effect was established between (b) (4) and epinephrine degradation. Topics discussed here:

1. (b) (4) [redacted]

2. (b) (4) [redacted]

3. sampling different parts of (b) (4) (b) (4) accomplished by Astra.

An HPLC method of determining the level of both epinephrine and lidocaine HCl was mentioned in passing by Dr. Warasvckewicz , with electrochemical detection of the epinephrine.

The end result of data presented to this point is that Astra feels the problem regarding (b) (4) content in rubber stoppers & cap liners has been conquered thru considerable effort by Astra with (b) (4) [redacted] The only reason the reviewing chemist can draw upon to contest this conclusion is the report from the Division of Biometrics (HFD-232) regarding the 6-16-77 statistical report by [redacted] (b) (4) as submitted by Astra to substantiate, or justify statistically, (b) (4) [redacted] Biometrics feels this study is inadequate. Astra has subsequently submitted another report which HFD-232 is reviewing.

It was pointed out by Astra that (b) (4) (b) (4) [redacted] with epinephrine than with the (b) (4) [redacted]

(b) (4) [redacted]

[redacted] (b) (4)

In any case, Astra is requesting approval of another rubber formulation for their dental cartridge cap liner, [redacted] (b) (4) Their reasons were stipulated, and are to be found in the S-016 supplement to NDA 6488 dated 9-13-78. [redacted] (b) (4) Dr. Blois expressed his desire to revise this request so that [redacted] (b) (4) will replace [redacted] (b) (4) after a certain time frame after approval. Dr. Blois will contact Mr. Koch early next week to verify the firm's thinking on this, and to be informed of other information that may be included in the S-016 supplement amendment.

Dr. Young then gave some comments from the firm's point of view. That is, that Astra has developed good scientific knowledge about this problem and has withdrawn lots from the market but that these formulations are used by other firms. He feels this problem should be addressed on an industry wide basis. The [redacted] (b) (4) representative said they have not informed other firms that use these rubber formulations about the problem because of the confidentiality that exists between them and Astra. Dr. Young said they tested other products and found low epinephrine values and particular matter. He feels the problem go beyond Astra.

Walt Brown said the Agency is monitoring other products in this area. Dr. Jerussi said he had no comment but would be sure that the minutes of this meeting including Dr. Young's comments are sent to the highest levels of the Compliance Office.

S. A. Koch

cc: NDA 6-488
HFD-160
DEC 15 1978
R/D by SKoch (HFD-160) 10/25/78
R/D Init by RJerussi 10/27/78
TYPED by JK 12/12/78
Doc. Rm 160
T. Byers, HFD-300
B. Loftus, HFD-320
D. Bryant, HFD-322
W. Brown, HFD-322
Bob Crowell, HFR-1140 BOS-DO

NDA 6-488

OCT 20 1978

Astra Pharmaceutical Products, Inc.
Attention: David W. Blois, Ph.D.
Neponset Street
Worcester, MA 01606

Gentlemen:

We acknowledge receipt of your supplemental application for the following:

Name of drug: Xylocaine(R) (lidocaine HCl) Injectable Solutions

NDA number: 6-488

Supplement number: S-019 Controls

Date of supplement: October 13, 1978

Date of receipt: October 16, 1978

All communications concerning this NDA should be addressed as follows:

Bureau of Drugs HFD-160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

Gary H. Boyer
Supervisory Consumer Safety Officer
Division of Surgical-Dental
Drug Products
Bureau of Drugs

cc: NDA 6-488 Orig.
(HFD-160
R/D by: DPaulsgrove 10/16/78(HFD-160)
R/D Init. by: GBoyer 10/17/78
RAJerussi Act. Dir. Oct. 10/18/78
F/T by mr 10/10/78 Doc. Room

SUPPLEMENT ACKNOWLEDGEMENT