

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-962/S-003

Trade Name: Toprol XL ER Tablets

Generic Name(s): (metoprolol succinate)

Sponsor: Astra Pharmaceutical Products, Inc.

Agent:

Approval Date: March 4, 1994

Indication: Provides for changes in the production method

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-962/S-003

Approval Letter(s)



NDA 19-962/S-003

Food and Drug Administration
Rockville MD 20857

Astra U.S.A., Inc.
Attention: Paul Damiani, Ph.D.
P.O. Box 4500
Westborough, MA 01581-4500

MAR - 4 1994

Dear Dr. Damiani:

Please refer to your February 17, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Toprol-XL (metoprolol succinate extended release) 50, 100, and 200 mg Tablets.

We also acknowledge receipt of your amendments and correspondence dated August 17, September 21 and October 29, 1993 and February 7, 1994.

The supplemental application provides for two changes in the production method influencing the composition of Toprol-XL tablets as follows:

1. Deletion of the maize starch, lactose powder, polyvidone components of the original excipient and replacement with
2. Addition of to the final tablet coating.

Please revise your dissolution specifications for Toprol-XL (using the same dissolution test consisting of USP apparatus II at 50 rpm in 500 ml of phosphate buffer pH 6.8) as follows:

1 hour: not more than 25%
4 hours: 20% to 40%
8 hours: 40% to 60%
20 hours: not less than 80%

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA

HF-2 (with labeling)

HFC-130/JAllen

HFD-110

HFD-110/CSO

HFD-80

HFD-230 (with labeling)

HFD-240 (with labeling)

HFD-638 (with labeling)

HFD-730 (with labeling)

HFD-110/ZMcDonald/2/16/94;2/18/94;2/18/94

sb/2/18/94;2/18/94;3/1/94

R/D: RMittal/2/22/94

RWolters/2/22/94

NMorgenstern/2/25/94

Approval Date: January 10, 1992

APPROVAL



NDA 19-962/S-003

OCT 6 1993

Astrá USA, Inc.
Attention: Joseph J. Anisko, Ph.D.
50 Otis Street
Westborough, MA 01581-4500

Dear Dr. Anisko:

Please refer to your February 17, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Toprol XL (metoprolol succinate extended release) 47.5, 95 and 190 mg Tablets.

We have completed our review of the biopharmaceutical section of your submission and have the following recommendations and requests:

1. The dissolution profiles for the new 74.5, 95 and 190 mg formulations are somewhat slower than the profile of the one lot of 95 mg from the old formulation. Please submit additional dissolution profiles for the 47.5, 95 and 190 mg from the old tablet formulations (and from the new formulations if available). These dissolution profiles, from several different lots, should provide information on the variability in the dissolution profiles of Toprol XL and whether the differences between the old and new formulations are due to variability or are real.
2. The following dissolution specification proposed in the original NDA seems too wide:

1 hour: not more than 25%
4 hours: 25 to 40%
8 hours:
20 hours: not less than 80%

If the 1:1 relationship in the in-vivo in-vitro correlation is taken into consideration, it is very possible to have lots that are more than different in their in-vivo profile. Thus, it is possible that two released lots that are on the upper and lower limits of the dissolution specifications (but still pass the dissolution specifications) may not be bioequivalent. In view of this possibility, please consider narrowing the dissolution limit specifications.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA

HFC-130/JAllen

HFD-110

HFD-110/CSO

HFD-80/DDIR

HFD-110/ZMcDonald/9/23/93;9/27/93

sb/9/24/93;10/5/93

R/D: RMittal/9/28/93

JShort for RWolters/9/27/93

NMorgenstern/10/1/93

INFORMATION REQUEST

NDA 19-962/S-003

AUG 9 1993

Astra Pharmaceutical Products, Inc.
Attention: Joseph J. Anisko, Ph.D.
500 Otis Street
Westborough, MA 01581-4500

Dear Dr. Anisko:

Please refer to your February 17, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for TOPROL-XL (metoprolol succinate extended release).

The supplemental application provides for minor composition change of metoprolol succinate extended release tablets.

We have completed our review and find the information presented is inadequate and the supplemental application is not approvable under section 505(b)(1) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. Regarding the amount of coating [] for the metoprolol succinate beads.

The amount of coating [] used for the metoprolol succinate beads [] You have mentioned in a footnote on page 10 that to obtain the correct content, dissolution rate and to allow for [

] from in-process control. The manufacturing and in-process control procedures did not include any instructions to [weight of the coating [] Please explain the procedures used in determining the amount of coating [] during these operations. [

] Please consider reducing this range to [] or present data to justify it.

2. Regarding [] of the metoprolol succinate beads.

The batches with the [] with other batches falling within these limits (C.4.b, page 29). The []

] that will meet the demands for direct approval. The process of [] batches to arrive at direct approval limit is not clear and requires clarification. For example, [

] can meet the approval limit of [] It is not clear if the

the batches is between the batches of a single main batch and/or between the batches of different batches.

3. Regarding the stability data.

The stability data in HDPE bottles for 47.5 mg and 190 mg tablets is for [] [] and for 90 mg tablets it is for [] [] The stability of the modified formulation has earlier been followed during a storage period of [] [] in [] [] glass bottles and [] [] blisters and HDPE bottles of other type than the US market containers. Before we can approve a [] [] expiry date, it will be necessary for us to compare the HDPE bottles used in the US with the HDPE bottles for which [] [] data was submitted. Therefore, please submit a description of both container-closure systems.

In addition, we are also waiting for the comments from Biopharmaceuticals Division on the dissolution data.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may withdraw this supplemental application.

Sincerely yours,

Robert J. Wolters, Ph.D.
Supervisory Chemist
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA

HFC-130/JAllen

HFD-110

HFD-110/CSO

HFD-83

HFD-110/RMittal

clb/8/5/93;8/9/93/N19962.NA

R/D init: RWolters/8/9/93

NOT APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-962/S-003

Chemistry Review(s)

FEB-7 1995

NDA 19-962

ASTRA

TOPROL-XL

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 19-962

REVIEW DATE: 07-FEB-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT S-003 (NC)	11-APR-94	12-APR-94	13-APR-94
SUPPLEMENT SLR-003	29-SEP-94	30-SEP-94	03-OCT-94
SUPPLEMENT S-005 (SCS)	19-DEC-94	20-DEC-94	XX-DEC-94

NAME & ADDRESS OF APPLICANT

ASTRA USA, Inc.
50 Otis Street
Westborough, MA 01581

DRUG PRODUCT NAME

Proprietary: TOPROL-XL™
Nonproprietary/USAN: Metoprolol Succinate extended release tablets
Code Name/#: H93/26 succinate salt
Chem.Type/Ther.Class: 5

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Beta-adrenergic blocker / Hypertension, Angina Post MI

DOSAGE FORM: Tablet, controlled Release formulation
STRENGTH: 50 mg 100 mg and 200 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

SUPPLEMENT PROVIDES FOR:

Revised dissolution specifications limit at 8 hours from [] to 40 - 60% and a change in the paddle agitation speed from [] rpm to 50 rpm.

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

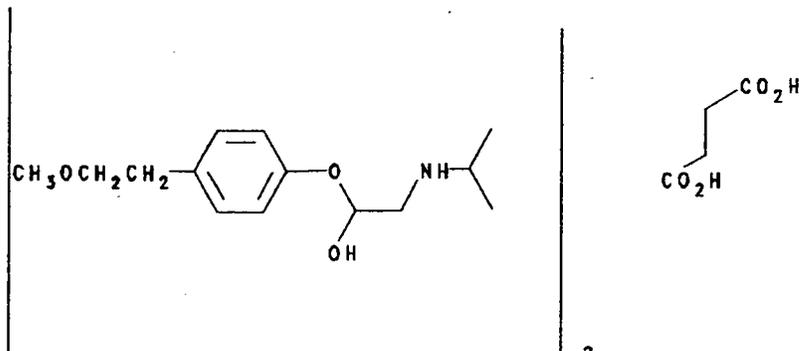
CHEMICAL NAME: (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol succinate (2:1) (salt)

CAS # :

MOLECULAR FORMULA: C₃₀H₅₀N₂O₆ · C₄H₆O₄

MOLECULAR WEIGHT: 653

STRUCTURAL FORMULA:



CONSULTS: None

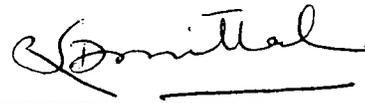
REMARKS/COMMENTS:

As per Agency's request the new dissolution specifications have been accepted by the applicant. But the applicant stated that if, the newer batches show a trend such that it appears that an agitation speed of 50 rpm may not satisfy the dissolution specification, they will contact the Agency to discuss the issue.

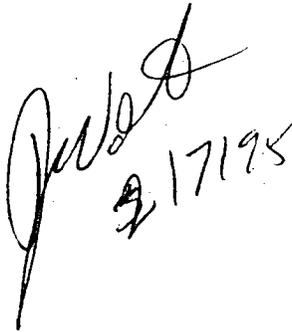
CONCLUSIONS & RECOMMENDATIONS:

Satisfactory and approval letter is being sent.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
R/D Init by: RWolters/



Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\19962\199628.005



2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: **19-962**

REVIEW DATE: 07-OCT-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT SCS-003(AC) (Response to S-003 deficiencies)	21-SEP-93	22-SEP-93	24-SEP-93

NAME & ADDRESS OF APPLICANT

ASTRA USA, Inc.
50 Otis Street
Westborough, MA 01581

DRUG PRODUCT NAME

<u>Proprietary:</u>	TOPROL-XL™
<u>Nonproprietary/USAN:</u>	Metoprolol Succinate extended release tablets
<u>Code Name/#:</u>	H93/26 succinate salt
<u>Chem.Type/Ther.Class:</u>	5

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Beta-adrenergic blocker / Hypertension, Angina Post MI

DOSAGE FORM: Tablet, controlled Release formulation
STRENGTH 50 mg 100 mg and 200 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

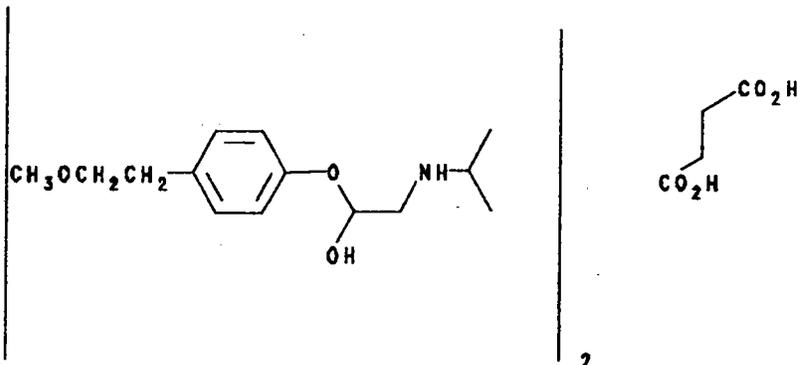
CHEMICAL NAME: (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol succinate (2:1) (salt)

CAS # :

MOLECULAR FORMULA: C₃₀H₃₅ON₂O₆·C₄H₆O₄

MOLECULAR WEIGHT: 653

STRUCTURAL FORMULA:



CONSULTS: Biopharm

REMARKS/COMMENTS:

The division of Biopharmaceutics needs to review additional dissolution data. The firm is being requested to submit additional data.

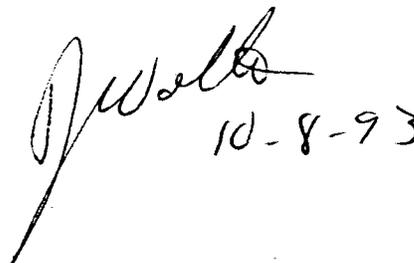
CONCLUSIONS & RECOMMENDATIONS:

After satisfactory review of the additional dissolution data by the Biopharmaceutics division the application will be approvable from a manufacturing and controls standpoint.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO
R/D Init by: RWolters/



Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\19962\19962SUP.R03



10-8-93

2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

NDA 19-962

ASTRA

TOPROL-XL

JUL 30 1993

DF

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 19-962

REVIEW DATE: 28-JUL-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT S-003	17-FEB-93	18-FEB-93	19-FEB-93

NAME & ADDRESS OF APPLICANT: ASTRA USA, Inc.
50 Otis Street
Westborough, MA 01581

DRUG PRODUCT NAME

<u>Proprietary:</u>	TOPROL-XL™
<u>Nonproprietary/USAN:</u>	Metoprolol Succinate extended release tablets
<u>Code Name/#:</u>	H93/26 succinate salt
<u>Chem.Type/Ther.Class:</u>	5

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Beta-adrenergic blocker / Hypertension, Angina Post MI

DOSAGE FORM: Tablet, controlled Release formulation
STRENGTH: 50 mg 100 mg and 200 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

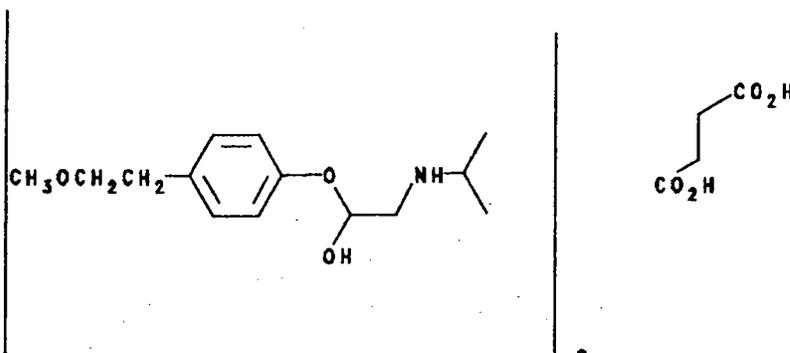
CHEMICAL NAME: (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol succinate (2:1) (salt)

CAS # :

MOLECULAR FORMULA: $C_{30}H_{35}ON_2O_6 \cdot C_4H_6O_4$

MOLECULAR WEIGHT: 653

STRUCTURAL FORMULA:



CONSULTS: Biopharm

REMARKS/COMMENTS:

There is a [] in the weight of the coating []. The stability data for the new composition is only for [] for the US approved HDPE bottles but up to [] in [] blisters and HDPE bottles other than US approved. Biopharm division has been requested for their comments on the new composition.

CONCLUSIONS & RECOMMENDATIONS:

The supplement needs some clarifications as per comments above. Specifics are contained in the draft letter to the sponsor. We are also waiting for the comments from the Biopharmaceuticals on the release rate of the new composition.

cc:

Orig. NDA

HFD-110/Division File

HFD-110/Ram Mittal/date

HFD-110/CSO

R/D Init by: RWolters/

Rammittal

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\19962\19962S.003

RWolters

7-30-93

17 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-962/S-003

**Clinical Pharmacology and Biopharmaceutics
Review**

NDA: 19-962
 Supplement SCS 003 (BB).
 Metoprolol Succinate ER tablets.
 47.5, 95 and 195 mg tablets.
 Toprol-XL.
 Astra Pharmaceuticals.

Submission Date: October 29, 1993.
 February 7, 1994.

Reviewer: Patrick J Marroum.

Type of submission: formulation change with request for an in vivo bioavailability study waiver.

BACKGROUND:

Toprol XL is a controlled release tablet formulation that was approved for marketing in the US at dosage strengths of 47.5, 95 and 190 mg.

The sponsor proposes 2 changes in the production method influencing the composition of this product. These changes consist of the deletion of maize starch, lactose powder, polyvidone [] of the original excipient [] and replacement with []

the addition of [] to the final tablet coating. The proposed formulation change is for the excipient [] and the tablet coat; the controlled release coating of the beads remains unchanged.

The sponsor presents additional data that was requested by the Division of Biopharmaceutics showing that the dissolution profile of the new formulation is not significantly different from the old formulation. Based on this fact, the sponsor is requesting an in vivo-bioavailability study waiver for all the approved strength tablets of Toprol XL.

Additionally, the sponsor is responding to the request for tightening the dissolution specification that was made in the Biopharmaceutics review dated September 21, 1993. The request was based on the data presented by the firm and also taking into account the 1:1 [] correlation that the sponsor presented.

RESULTS:

Figure 1 shows the dissolution profile for the old and new 47.5, 95 and 190 mg formulations in the approved dissolution medium (500 ml phosphate buffer pH 6.8). Figure 2 shows the dissolution profile of the 95 mg tablet (old and new) in 500 ml phosphate buffer pH 4 while Figure 3 shows the dissolution profile of all the tablet strengths in 500 of simulated gastric fluid without enzymes at pH 1.2. Figure 4 gives the dissolution profile of the coated beads in the approved medium using a USP type II apparatus at a speed of [] rpm (note that the approved speed is 50 rpm). Table 1 gives the composition of the old and new formulations.

It can be seen from the results that the new formulation has a dissolution profile that is very similar to the dissolution profile of the old formulation in both phosphate buffer pH 6.8 and 4. However, the dissolution profiles in an acidic medium of pH 1.2 for the different strengths are

somewhat different without any consistent trend. This difference is most probably due to variability of the dissolution in this medium. The results also show that the beads dissolve at a rate slower than their corresponding tablets.

COMMENTS:

1-Even though the dissolution profiles of the old and new formulations are somewhat more variable in an acidic medium of pH 1.2, it is not expected that this variability will result in a different in vivo profile between the old and new formulation. This is due to the fact that the approved dissolution method was able to differentiate between formulations with different release characteristics and in this case the dissolution profiles of the old and new formulation in the approved media, where the in vivo ^{was established} in vitro correlation, were identical.

2-The beads show a dissolution profile that is slower than their corresponding tablets. Nevertheless, these results would not have any effect on the in vivo performance of the tablet because the beads used in the old and new formulations are identical.

3- The sponsor is objecting to the request for tightening the dissolution specifications arguing that these specifications were determined based on dissolution of individual lots. Thus if the specifications were tightened in a way that one would not get more than [] difference between the upper and lower specification limits, some individual tablets would fail and the sponsor would need to go to the level II testing according to the USP acceptance criteria.

This argument is not valid because:

1-In the presence of a 1:1 [] in vivo in vitro correlation, one would not look at the profiles of individual tablets and set specifications that are met by each and every tablet. The correlation between the in vitro dissolution and the in vivo profile should be taken into account. Specifications should be set in a way to assure bioequivalence among all released batches (even though these specifications might not be met by each and every tablet and in some cases a level II testing might be needed). This way, the in vitro dissolution test is considered more meaningful.

4-Dissolution specifications that are set in a way that all individual data pass is considered too loose and thus will not be able to pick up any real differences among batches. Looking at the dissolution results for the new metoprolol formulation, one could see that the differences between the minimum and maximum dissolution value for each batch does not exceed [] Thus it is possible to tighten the specifications without having to fail any of the tested batches (even though in some cases a level II testing might be required).

RECOMMENDATION:

The following recommendations are made by the Division of Biopharmaceutics:

1-An in vivo bioavailability study waiver is granted for the 47.5, 95 and 190 mg modified composition tablets.

2-The dissolution specifications for Toprol XL using the same dissolution test consisting of USP apparatus II at 50 rpm in 500 ml of phosphate buffer pH 6.8 should be amended to the following:

-1 hour: not more than 25 %.

-4 hours: 20 to 40 %.

-8 hours: 40 to 60 %.

-20 hours: not less than 80 %.


Patrick J Marroum Ph.D. 2/14/94

RD/FT initialed by Ameeta Parekh Ph.D. Ameeta Parekh 2/14/94

cc: NDA 19-962, HFD 110, HFD 426 (Marroum, Fleischer, Malinowski), HFD 340 (Vishwanathan), Chron, Drug, CR, HFD 19 (FOI), Reviewer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-962/S-003

Administrative/Correspondence Reviews

MAY - 3 1994

Minutes of a Teleconference
Astra and FDA
April 26, 1994

NDA# 19-962/S-003 Toprol XL (metoprolol succinate) Extended-Release Tablets

FDA Participants:

Robert Wolters, Ph.D. Supervisory Chemist, Div. of Cardio-Renal Drug Products,
HFD-110
Ram Mittal, Ph.D. Chemist, HFD-110
Patrick Marroum, Ph.D. Biopharmaceutist, Division of Biopharmaceutics, HFD-426
Zelda McDonald CSO, HFD-111

Astra Participants:

Dennis Bucceri Senior Director, Regulatory Affairs
Paul Damiani, Ph.D. Assistant Director, Regulatory Affairs

Background:

On March 4, 1994 we approved 19-962/S-003 that provided for a change in the formulation of Toprol-XL (metoprolol succinate) Extended-Release Tablets. In the approval letter we requested that Astra revise the dissolution specifications for Toprol-XL using a dissolution test consisting of USP apparatus II at 50 rpm in 500 ml of phosphate buffer pH 6.8 as follows:

1 hour:	not more than 25%
4 hours:	20% to 40%
8 hours:	40% to 60%
20 hours:	not less than 80%

In a letter dated April 11, 1994, Astra state that they would change their dissolution specifications with regard to percent dissolved at the indicated time points we requested, however, they did not recall discussing the necessity of lowering the paddle agitation speed from — rpm to 50 rpm. They also stated that the methods package that was submitted in the original NDA and approved by the Cardio-Renal Drug Products Division indicated that Astra was using a paddle agitation speed of — rpms. Dr. Marroum said that the Biopharmaceutical review of the original NDA was sent to the firm before approval, and the reviewer recommended a paddle speed of 50 rpm. Dr. Marroum based his approval of supplement 3 on a paddle speed of 50 rpm not — rpm. The purpose of this teleconference was to discuss how to handle this matter.

Teleconference:

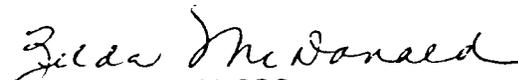
Astra reiterated that the methods package in the NDA indicated a paddle speed of — rpm and that is what the firm has been using. Dr. Marroum pointed out that the paddle speed recommended in the Biopharmaceutical review is what is to be followed, not what is submitted in the NDA. Dr. Marroum did not understand why Astra had a problem using 50 rpm since the correlation was good at that speed.

Astra said . [1 50 rpm and asked if they could continue to test at 50 and — rpm. Dr. Marroum said that the Bio waiver that was granted for supplement 3 was based on 50 rpm so in order to market the new formulation the paddle speed would have to be at 50 rpm or else he would have to recalculate everything, and they might lose the waiver.

Astra said they would test at 50 rpm on release and — rpm on stability and tell the people in Sweden this. They also would not import any lots that did not meet the 50 rpm speed and continue to test until they had enough batches.

Dr. Wolters asked Astra to figure out how many batches they would need to test and how long it would take to produce those batches. Astra said they would call with that information next week.

NB: Astra called back on April 29, 1994 stating that they would need — batches and the information would be generated by the end of September 1994 (50 rpms on release and — rpms on stability). I informed Astra that they could report it as a Special Supplement - Changes Being Effectuated (per Dr. Wolters).


Zelda McDonald, CSO

cc: Orig. NDA 110
HFD-111/McDonald
HFD-111/Benton
HFD-426/Parekh
Drafted 5/3/94

RD: Marroum 5/3/94
Wolters 5/3/94

FAX



FROM	DATE
Dr. Paul Damiani	07/26/93
DEPARTMENT	FAX NO.
RX - CDMRA	508 366 1074
TO	FAX NO.
Dr. Ram Mittal	301 443 9283
SUBJECT	PAGES
Toprol-XL NDA# 19-962	2

Dear Dr. Mittal,

Attached is a copy of page 03 001 034 from Amendment #3 to NDA# 19-962 submitted to the Division of Cardio-Renal Drug Products on November 2, 1990. As part of this amendment, the role of [] in the bead formulation process was explained. I hope this explanation satisfactorily answers your questions concerning the use of [] in the manufacture of Toprol-XL tablets. Please contact me at (508) 366-1100 Ext 4772 if you have any additional questions.

Sincerely,

Paul Damiani
Paul Damiani

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4800
Westborough, MA 01581-4800

OFFICE:
50 Otis Street
Westborough, MA

TEL:
508-366-1100

FAX:
508-366-7406
TELEX:
6810105-Cable/Astrapharm

Amendment 3

IV. Response to FDA Request - Chemistry, Manufacturing and Controls Section

Question 4.d.

Please explain the role of [] in the bead formulation process.

Answer:

As previously discussed []

[] of metoprolol succinate bulk drug substance. After []

[] As described in the manufacturing process (sec 03/vol 003/pp 114 and 169 in original submission dated December 22, 1989) the [] drug substance can either [] the production of metoprolol succinate beads. []

[] If [] metoprolol succinate is used in [] process,

[] However, []

[] As shown in the process validation (sec 03/vol 003/p 195 in original submission dated December 22, 1989) the manufacture of metoprolol succinate beads [] is very reproducible. The []

highest recommended daily dose (400 mg). Since no additional [] is used in the manufacturing process, it has not been considered necessary to include a test [] in the control of the finished product.