

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
19-962/S-013**

Administrative Documents

ITEM 13
PATENT INFORMATION

I. Patent Information

The patent information for Toprol-XL is provided in this section. Five (5) patents have been identified as pertinent to Toprol-XL and its indication for the treatment of cardiovascular disorders generally.

Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2).

<u>Patent Number</u>	<u>Patent Expiration Date</u>	<u>Type of Patent</u>	<u>Patent Owner</u>	<u>Authorized Representative to Receive Notice of Patent Certification</u>
4,927,640	May 22, 2007	drug product	Aktibolaget Hässle	AstraZeneca LP
4,957,745	September 18, 2007	drug product; method of use	Aktibolaget Hässle	AstraZeneca LP
5,001,161	March 19, 2008	drug product	Aktibolaget Hässle	AstraZeneca LP
5,081,154	January 14, 2009	drug substance	Aktibolaget Hässle	AstraZeneca LP
5,246,714	September 21, 2010	drug product	Aktibolaget Hässle	AstraZeneca LP

APPEARS THIS WAY
ON ORIGINAL

II. Patent Declaration Statement

DECLARATION

The undersigned declares that U.S. Patent Numbers 4,927,640; 4,957,745; 5,001,161; 5,081,154; and 5,246,714 cover the formulation, composition, and/or method of use of Toprol-XL (metoprolol succinate). Toprol-XL (metoprolol succinate) is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.



Elliott T. Berger, Ph.D.
Vice President, Regulatory Affairs
AstraZeneca LP

ITEM 14
PATENT CERTIFICATION

NOT APPLICABLE

This application is not a 505(b)(2) application, therefore, the Patent Certification as described under 21 CFR §314.50 is not required.

Trade Name: Toprol XL Generic Name: metoprolol succinateApplicant Name: AstraZeneca HFD # 110Approval Date If Known February 5, 2001**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.)

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
The number of years was not mentioned.

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / ___ / NO / X /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/_/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/_/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SH-MET-0024, SH-AHS-0001(RESOLVD), S-996 and SH-MET-0022

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1,2 YES /___/ NO /_X_/

Investigation #3,4 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1,2 YES /___/ NO /_X_/

Investigation #3,4 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

See #2(c) _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 & 2 SH-MET-0024 and S-996

IND YES / / NO / / Explain: _____

Investigation #3 SH-AHS-0001

IND (IND) YES / / ! NO / / Explain: _____

Investigation #4 SH-MET-002 -Studies done in Europe

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

Signature: Zelda McDonald
Title: Regulatory Health Project Manager

Date February 5, 2001

Signature of Office/
Division Director

Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

ITEM 16

DEBARMENT CERTIFICATION

1.0 DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k)(1)], we hereby certify that, in connection with this application, AstraZeneca LP (Formerly Astra Pharmaceuticals L.P.) has not and will not use in any capacity the services of any person debarred under subsection 306 (a) or (b) of the Act.

19.0. Other (Financial Certification)

Reference is made to our letter dated April 9, 1999 to the FDA, Office of External Affairs, wherein AstraZeneca LP proposed a plan for providing financial disclosure/certification statements for NDA 19-962 supplement. AstraZeneca LP proposed in the letter, that since the supplemental NDA relied on a single very large, multi-center trial SH-MET-0024 (MERIT-HF) to support the approval of a new indication (i.e., treatment of heart failure), the large multi-center, randomized, double-blind design of this trial, in which all-cause mortality and all-cause mortality in combination with all-cause hospitalization were the primary endpoints and all endpoints were determined by an Independent Endpoint Committee, minimized the potential for bias of clinical investigators. Recognizing the role of the Independent Endpoint Committee and the Independent Safety Committee, AstraZeneca LP proposed to include financial disclosure/certification statements for the members of both committees with the supplement to NDA 19-962. Reference is also made to a May 20, 1999 telephone conversation between Steven J. Miller, Ph.D, of AstraZeneca LP, and Linda Carter, FDA, during which Ms. Carter stated that she and Dr. Temple had reviewed AstraZeneca's April 9, 1999 proposal and found that the suggestion to provide Disclosure/Certification for the Independent Endpoint and Safety Committees rather than for each of the 313 investigators was reasonable and acceptable.

Thus, based on the sponsor's agreement as noted above, information was collected regarding financial interests described in 21 CFR § 54.2(a) compensation affected by the outcome of clinical studies, 54.2(b) equity interests, 54.2(c) proprietary interests and 54.2(f) significant payments from the members of the Independent Endpoint and Safety Committees. It was determined that there are no disclosable financial interests. Therefore, Form FDA 3454 is being provided along with the list of members of the Independent Endpoint and Safety Committee members.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

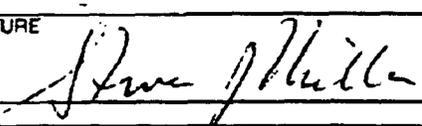
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Steven J. Miller, Ph.D.	TITLE Director, Regulatory Liaison
FIRM/ORGANIZATION AstraZeneca LP	
SIGNATURE 	DATE September 10, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Independent Endpoint Committee

Associate Professor Ola Samuelsson, MD, PhD
Sahlgrenska University Hospital, Gothenburg, Sweden

Dr. Seppo Lehto, MD, PhD
Kuopio University Hospital, Finland

Professor Wolfgang Motz, MD, PhD
Ernst-Morita-Arndt-Universitat, Germany

Dr. Jan Willem Viersma, MD
NL-9752 LK Haren Gr, The Netherlands

Professor Pal Karpati, MD
Budapest, Hungary

Independent Safety Committee

Professor Kanu Chatterjee, MD, FRCP
University of California, San Francisco, CA

Professor David DeMets, MD
University of Wisconsin Medical School, Madison, WI

Professor Desmond Julian, MD
London NW# 5RN, United Kingdom

Jan M. Feyzi, MS
University of Wisconsin – Madison, WI

RHPM Overview of NDA 19-962/S-013
Toprol-XL (metoprolol succinate) Extended Release Tablets
June 27, 2000

Type: S
Receipt Date: September 10, 1999
User Fee Goal Date: July 10, 2000 (10 Month)
September 10, 2000 (12 Month)

Background

The original metoprolol succinate application was approved on January 10, 1992 for treatment of hypertension and angina. This supplemental application was submitted on September 10, 1999 for the treatment of congestive heart failure (CHF).

Medical Review

In his review dated February 9, 2000, Dr. Duarte recommended that this supplement be approved. He recommended the following labeling changes:

1. Under the Heart Failure/Clinical Trials section, the following should be added to the end of the first paragraph:

2. Under the Heart Failure/Clinical Trials section, the following should be added to the end of the fourth paragraph:

3. Under the Adverse Reactions/Miscellaneous section, the following should be added to the end of the last paragraph:

Medical Team Leader Memo

In his memo dated June 22, 2000, Dr. Stockbridge stated that metoprolol should be approved for the indication not tainted by the US vs non-US heterogeneity. The clinical trials section should contain a description of the mortality results overall and of the discrepant US findings. Advertising of the mortality data should contain fair balance by showing the US results as well.

Deputy Division Director Memo

In his memo dated May 16, 2000, Dr. Fenichel recommended that Toprol-XL be approved for use in the treatment of congestive heart failure with the indication that when it is so used in patients who are receiving optimal therapy with ACE inhibitors and diuretics, it reduces the combined incidence of death and hospitalization.

The labeling of Toprol-XL should describe the MERIT study, including the fact that the overall effect of active treatment was a reduction in all-cause mortality. This description should include language to the effect that:

-
-
-

Division Director Memo

In his memo dated June 26, 2000, Dr. Lipicky stated that the overall trial result (either endpoint) is as strong as he had seen, there is no doubt that metoprolol is useful in the treatment of patients with chronic systolic heart failure when added to any and/or all conventional therapies (except carvedilol). So it is approvable.

The only question is what to say in labeling regarding the U.S. vs Europe trial. His suggestion is that nothing be said at all. Indications should read essentially like carvedilol's, the only other beta-blocker approved for heart failure. His suggestion is:

INDICATIONS

Trade Name is .

Trade Name may

He would avoid much attention to the U.S. vs Europe trial in the description of the clinical trial.

CLINICAL TRIALS

Dr. Lipicky agreed with AstraZeneca's request for a waiver of the Pediatric Use Information requirement. A copy of their request can be found under the Pediatric Page tab.

Statistical Review

In his review dated May 30, 2000, Dr. Cui concluded that the MERIT study on its own demonstrated a beneficial effect of metoprolol in treating patients with CHF. The benefit of metoprolol treatment in mortality, however, was limited to only European patients with apparently no effect on mortality in U.S. patients. He questioned whether or not a mortality indication should be granted to metoprolol because of the uncertainty of the drug's effect in U.S. patients. He made no labeling recommendations.

Biopharmaceutical Reviews

In her review dated February 17, 2000, Dr. Nguyen, stated that NDA 19-962/S-013 was acceptable to the office of Clinical Pharmacology and Biopharmaceutics. She recommended the following labeling changes:

1. Under the Clinical Pharmacology/Pharmacokinetics section, the following should be added after the second sentence, second paragraph:

Metoprolol is administered as a racemic mixture of R- and S- enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.

2. The following should be added to the Drug Interactions section:

[DRAFT LABELING]

In her review dated February 3, 2000, Dr. Zhao concluded that the 25 mg CR tablets to-be-marketed have comparable dissolution performance to the reference tablets (50 mg CR commercial tablets) and to the 25 mg CR tablets used in a Phase 3 study. All tablets tested met the specifications for Toprol-XL tablets.

For the drug product dissolution test on the metoprolol CR/XL 25 mg to-be-marketed tablet, the currently established dissolution method and specifications should be applied as for the commercially available metoprolol CR/XL 50, 100 and 200 mg tablets.

Clinical Inspection

In his clinical inspection summary dated April 7, 2000, Dr. U concluded that the data from all of the subjects in the Kecskemet, Hungary center and the two centers in the U.S. can be used for evaluation of the MERIT study.

Pharmacology Review

In his review dated February 1, 2000, Dr. DeFelice recommended approval from the pre-clinical standpoint. No new safety pharmacology or toxicology studies were performed, or are needed, for the proposed CHF indication. The Sponsor had previously established that, at least in the healthy anesthetized dog, direct myocardial depressant activity occurs only at an exposure several orders of magnitude greater than that affording targeted pharmacological activity.

Chemistry Review

In his review dated June 27, 2000, Dr. Mittal recommended approval.

The expiry date of _____ used for the approved strengths will also be used for the 23.75 mg tablets.

The routine stability program should include a _____]

It is recommended that the storage statement, [

in the package insert and container labels for all strengths of the metoprolol succinate tablets be replaced by the following:)

“Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room temperature]

A change in name of AstraUSA to AstraZeneca should be made in the labeling.

EER – For alternate packaging facility is acceptable.

Environmental Assessment: Categorical exclusion.

Methods Validation: Pending

CSO Summary

To my knowledge there are no issues that would prevent action on this application.

[/S/]
Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

Meeting Minutes

Meeting Date: October 23, 2000
Requested: September 15, 2000
NDA#: 19-962/S-013 Metoprolol XL (metoprolol succinate) for CHF
Sponsor: AstraZeneca
Type of Meeting: Labeling
Classification: C

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Steven Miller, Ph.D.

FDA Participants:

Robert Temple, M.D.	Director, ODE 1, HFD-101
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Cristobal Duarte, M.D.	Medical Officer, HFD-110
Robert O'Neill, Ph.D.	Director, Office of Biostatistics, HFD-700
Charles Anello, Ph.D.	Deputy Director, HFD-700
George Chi, Ph.D.	Director, Division of Biometrics I, HFD-710
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Lu Cui, Ph.D.	Statistician, HFD-710
Nhi Nguyen, Ph.D.	Pharmacokineticist, HFD-860
Zelda McDonald	RHPM, HFD-110

Astra Zeneca:

Hamish Cameron, M.D.	V.P., Head of Global Cardiovascular Therapy Area
Ronald Krall, M.D.	Sr. V.P, Clinical Development and Medical Affairs
Gunnar Olsson, M.D., Ph.D.	Vice President, Global Cardiovascular Medicine
Mark Scott, Ph.D.	Executive Director, Quantitative Decision Sciences
Anthony Rogers	Vice President, Regulatory Affairs
Steven Miller, Ph.D.	Executive Director, Cardiovascular Regulatory Affairs
John Wikstrand, M.D., Ph.D.	Senior Medical Advisor

Background

AstraZeneca submitted an efficacy supplement on September 10, 1999 to their Toprol XL NDA for the use of metoprolol succinate in the treatment of congestive heart failure (CHF), with a claimed effect on both a combined endpoint of death plus hospitalization and mortality alone. The effectiveness of the drug is supported by one international controlled clinical trial, SH-MET-0024-MERIT-HF (MERIT). This study included 4000 patients, 1000 of whom were from the U.S. Although both endpoints showed a highly statistically significant benefit of Toprol XL, there was no survival benefit seen in the subset of U.S. patients. An approvable letter issued on July 10, 2000 that included a marked-up package insert.

A labeling meeting was held on July 24, 2000 between AstraZeneca and the Agency wherein all issues were resolved except for the wording of the indications section of the package insert and inclusion of specific U.S. data. AstraZeneca requested this meeting to discuss the unresolved issues.

**APPEARS THIS WAY
ON ORIGINAL**

Meeting

The Agency believed that the heart failure indication for Toprol-XL should read:

Toprol-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, Toprol-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

AstraZeneca believes the indication should reflect the overall results for the prespecified primary endpoints and therefore should be modified to:

[DRAFT LABELING]

- AstraZeneca had been denied a mortality indication because of the discrepant results between the U.S. and the rest of the study sites. The Agency did not believe the indications section should be changed.

AstraZeneca believes that the inclusion of the specific U.S. data in the label is not helpful to the prescribing physician, other health care professionals and patients. AstraZeneca believes that the scientists within the Agency and the Advisory Committees are able to evaluate better an issue as complicated as the interpretation of subgroup results and the approval of this supplement should reflect the conclusion of this evaluation, not provide the detailed and contradictory data for re-evaluation by each prescriber. The clinical trials section should include a description of the overall study results from the MERIT study.

- The Agency was not willing to remove the U.S. data tables because it was believed the tables represented "truth in labeling," but agreed to the following:
 1. The p-values in those tables can be removed,
 2. The sentence, "Post-hoc subgroup analyses of this kind can be very difficult to interpret" could be added before the last sentence of the wording before the Overall Results in MERIT-HF table and,
 3. The sentence, "Analyses of U.S. subjects and women was carried out because these subjects represent almost 25% of the overall population" could be added at the end of the wording before the Overall Results in MERIT-HF table.
- The Agency also suggested that AstraZeneca conduct a focus group study to determine how the labeling would be interpreted. The intent of the labeling is not to dissuade people from using the drug. The Agency would be interested in participating in the design of such a study.
- The Agency invited AstraZeneca to propose further alternatives.

Signature minutes preparer: _____

15/ 11/6/00

Concurrence, Chair: _____

15/

Orig. NDA
HFD-110
HFD-110/McDonald
HFD-110/Matthews
HFD-101/R Temple

Drafted 10/26/00	Finaled 11/2/00
RD:	
Temple	10/30/00
Throckmorton	10/27/00
Stockbridge	10/27/00
Duarte	10/27/00
Cui	10/27/00
Hung	10/27/00
O'Neill	
Anello	
Chi	
Nguyen	10/27/00

Entered into DFS 10/5/00 MFC Donald

SEP 25 2000

Confirmation of Meeting

Drug: Toprol XL (metoprolol succinate) NDA 19-962/S-013
Sponsor: AstraZeneca
Date Requested: September 15, 2000
Date Confirmation Faxed: September 25, 2000
Type: Labeling
Classification: C

Meeting Date: October 23, 2000
Meeting Time: 3:30 pm
Location: Conference Room "F," Sixth Floor, Woodmont Office Complex 2
1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Rachel Behrman, M.D.	Deputy Director, ODE I, HFD-101
Douglas Throckmorton, M.D.	Deputy Director, Div. Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
Cristobal Duarte, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Lu Cui, Ph.D.	Statistician, HFD-710
Nhi Nguyen, Ph.D.	Pharmacokineticist, HFD-860
Andrew Haffer	CSO, DDMAC, HFD-40
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Zelda McDonald	Regulatory Health Project Manager, HFD-110

cc:
Orig. NDA
HFD-110/McDonald/Matthews

JUL 5 2000

Minutes of an In-House Meeting

Date: June 8, 2000
NDA#: 19-962/S-013
Drug: Toprol XL (metoprolol)
Sponsor: AstraZeneca
Type of Meeting: To discuss whether the application should be presented before the July 20, 2000 Cardiac and Renal Drugs Advisory Committee
Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Zelda McDonald

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Raymond Lipicky, M.D.	Director, HFD-110
Steven Fredd, M.D.	Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Cristobal Duarte, M.D.	Medical Officer, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Zelda McDonald	RHPM, HFD-110
David Roeder	RHPM, HFD-110
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Charles Anello, Ph.D.	Deputy Director, HFD-700
Satya Dubey, Ph.D.	Associate Director, HFD-700
Lu Cui, Ph.D.	Statistician, HFD-710
Kooros Mahjoob, Ph.D.	Acting Deputy Director, HFD-710
Jim Hung, Ph.D.	Acting Team Leader, Statistics, HFD-710
George Chi, Ph.D.	Director, Division of Biometrics I, HFD-710

Background:

AstraZeneca submitted an efficacy supplement on September 10, 1999 to their Toprol XL NDA for the use of metoprolol succinate in the treatment of congestive heart failure (CHF), with a claimed effect on both a combined endpoint of death plus hospitalization and mortality alone. The effectiveness of the drug is supported by one international controlled clinical trial, SH-MET-0024-MERIT-HF (MERIT). This study included 4000 patients, 1000 of whom were from the U.S. Although both endpoints showed a highly statistically significant benefit of Toprol XL, there was no survival benefit seen in the subset of U.S. patients.

A meeting was held with AstraZeneca on April 11, 2000 to discuss the Division's intent to take this application before the July 2000 advisory committee meeting. Although the Division believes effectiveness is established for the combined endpoint of death plus hospitalization and overall for mortality, there is a question about how to interpret the apparent lack of a survival effect in the domestic population. AstraZeneca met with the Division on May 9, 2000 and again with the Office on May 22, 2000 to discuss the need for taking Metoprolol before the Advisory Committee in July, 2000.

MAY 31 2000

Meeting Minutes

Meeting Date: May 22, 2000
Requested: April 12, 2000
NDA#: 19-962/S-013 Metoprolol XL (metoprolol succinate) for CHF
Sponsor: AstraZeneca
Type of Meeting: Discuss taking metoprolol before the Advisory Committee in July 2000
Classification: C (Guidance)

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Steven Miller, Ph.D.

FDA Participants:

Robert Temple, M.D.	Director, ODE 1, HFD-101
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Cristobal Duarte, M.D.	Medical Officer, HFD-110
Lu Cui, Ph.D.	Statistician, HFD-710
Natalia Morgenstern	Chief, Project Management Staff, HFD-110
Zelda McDonald	RHPM, HFD-110

Astra Zeneca:

Steven Miller, Ph.D.	Executive Director, Cardiovascular Regulatory Affairs
John Wikstrand, M.D., Ph.D.	Senior Medical Advisor
Michael Klibaner, M.D., Ph.D.	Director, Clinical Research
Jennifer Sugg, M.S.	Senior Statistical Scientist
Patricia Patterson	Regulatory Project Manager
Anthony Rogers	Vice President, Regulatory Affairs
Robert Davis, Ph.D.	Biostatistics Leader

Background

AstraZeneca submitted an efficacy supplement on September 10, 1999 to their Toprol XL NDA for the use of metoprolol succinate in the treatment of congestive heart failure (CHF), with a claimed effect on both a combined endpoint of death plus hospitalization and mortality alone. The effectiveness of the drug is supported by one international controlled clinical trial, SH-MET-0024-MERIT-HF (MERIT). This study included 4000 patients, 1000 of whom were from the U.S. Although both endpoints showed a highly statistically significant benefit of Toprol XL, there was no survival benefit seen in the subset of U.S. patients.

A meeting was held with AstraZeneca on April 11, 2000 to discuss the Division's intent to take this application before the July 2000 advisory committee meeting. Although the Division believes effectiveness is established for the combined endpoint of death plus hospitalization, there is a question about the survival benefit because of the lack of apparent effect in the domestic population. AstraZeneca met with the Division on May 9, 2000 to discuss the need for taking Metoprolol before the Advisory Committee in July, 2000. AstraZeneca requested this meeting to further discuss the view of the Division that NDA 19-962/S-013 should be presented to the Advisory Committee in July, 2000.

Meeting

AstraZeneca stated that the subgroup analysis issue is complicated and is not unique to MERIT. They believed it would be very difficult to assemble the necessary data and expertise to do the subject justice for the July meeting. As they believed this was not an approvability issue, they did not think it was appropriate to delay action on their application in order to go before the Advisory Committee.

Z. McDonald

MAY - 9 2000

Meeting Minutes

Meeting Date: May 9, 2000
Requested: April 19, 2000
NDA#: 19-962/S-013 Metoprolol XL (metoprolol succinate) for CHF
Sponsor: AstraZeneca
Type of Meeting: Discuss taking metoprolol before the Advisory Committee in July 2000
Classification: C (Guidance)

Meeting Chair: Raymond Lipicky, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: Steven Miller, Ph.D.

FDA Participants:

Raymond Lipicky, M.D. Director, Division of Cardio-Renal Drug Products, HFD-110
Robert Fenichel, M.D., Ph.D. Deputy Director, HFD-110
Cristobal Duarte, M.D. Medical Officer, HFD-110
Sol Sobel, M.D. Office of Regulatory Review
Jim Hung, Ph.D. Team Leader, Statistics, HFD-710
Lu Cui, Ph.D. Statistician, HFD-710
Zelda McDonald RHPM, HFD-110

Astra Zeneca:

Steven Miller, Ph.D. Executive Director, Cardiovascular Regulatory Affairs
John Wikstrand, M.D., Ph.D. Senior Medical Advisor
Michael Klibaner, M.D., Ph.D. Director, Clinical Research
Jennifer Sugg, M.S. Senior Statistical Scientist
Patricia Patterson Regulatory Project Manager

Background

AstraZeneca submitted an efficacy supplement on September 10, 1999 to their Toprol XL NDA for a new use of metoprolol succinate in the treatment of congestive heart failure (CHF). AstraZeneca asserts that the effectiveness of the drug is supported by one international controlled clinical trial, SH-MET-0024-MERIT-HF (MERIT). This study consisted of \ patients, \ of whom were from the U.S. The integrated summary of safety was derived from 4 studies as well as marketing experience adverse event reports.

A meeting was held with AstraZeneca on April 11, 2000 to discuss the Division's desire to take this application before the July 2000 advisory committee meeting. Statistical evaluation using subgroup analysis showed that there is no statistical significance for effectiveness of the drug in the U.S. population for the CHF indication. AstraZeneca requested this meeting as a follow-up to the May 1, 2000 Advisory Committee meeting wherein the ramipril HOPE study subgroup analysis was discussed.

Meeting

AstraZeneca believed that the outcome of the May 1, 2000 meeting did not warrant taking metoprolol succinate to the July 2000 Advisory Committee meeting. Dr. Lipicky stated that he initially believed the same, but found an increased interest among the Division reviewers in taking metoprolol before the Committee. The Division reviewers believe that the difference in effectiveness between the European and U.S. patients should be discussed in an open forum. The Committee discussion of HOPE did not address what to do if the point estimate is adverse for the subgroup (U.S.) for which the drug is to be approved.

Z. McDonald

APR 11 2000

Meeting Minutes

Meeting Date: April 11, 2000
NDA: 19-962/S-013
Submission Date: 10 September 1999
Sponsor: AstraZeneca

FDA Participants

Raymond Lipicky, M.D.	Director, DCRDP, HFD-110
Douglas Throckmorton, M.D.	Medical Officer
Maryann Gordon, M.D.	Medical Officer
Cristobal Duarte, M.D.	Medical Reviewer
Lu Cui, Ph.D.	Statistician
Natalia A Morgenstern	Chief, Project Management Staff

AstraZeneca

Steven J. Miller, Ph.D.	Executive Director, Cardiovascular Regulatory Affairs
Howard Hutchinson, M.D., F.A.C.C.	Therapeutic Area Medical Leader
John Wikstrand, M.D., Ph.D.	Senior Medical Advisor
Mark Scott, Ph.D.	Quantitative Decision Sciences Leader
Georgina Bermann, Ph.D.	Global Product Statistician
Jennifer Sugg, M.S.	Biostatistician
Patricia Patterson	Regulatory Project Manager

SUBJECT: NDA 19-962/S-013 TOPROL -XL (metoprolol succinate) Extended Release Tablets

Background:

AstraZeneca submitted a supplemental application on September 10, 1999 to their Toprol NDA for a new use of metoprolol succinate in the treatment of congestive heart failure. The submission consisted of results from several studies conducted outside the U.S. The firm asserts that the effectiveness of the drug is supported by one international controlled clinical trial (SH-MET-0024 - MERIT-HF). This study consisted of patients, of whom were from the U.S. The integrated summary of safety was derived from 4 studies as well as marketing experience adverse event reports.

This meeting was requested by AstraZeneca to discuss the division's desire to take this application before the July 2000 advisory committee meeting. Statistical evaluation using subgroup analysis showed that there is no statistical significance for effectiveness of the drug in the US population.

Meeting

After normal introductions Dr. Steve Miller started the meeting by saying that AstraZeneca requested this meeting to discuss three things:

1. The issues to be discussed at the advisory committee meeting.
2. The briefing package for the advisory committee.
3. Whether the committee is going to change from its current membership by the time the July meeting is held.

Dr. Lipicky stated that the issues involving the metoprolol are still evolving in the division. He wanted to take this drug to the advisory committee meeting to discuss two issues; one is how to interpret results of a subgroup analysis that was not pre-defined. Second, he wanted to discuss the role of beta-blockers in congestive heart failure (CHF).

He then proceeded to tell the firm about the new rules involving advisory committee meetings all of which are in the published MAPP on FDA's website. In addition, he stated that it is important that the committee focus on the issues and not disagreements about numbers, so that our "numbers" should not differ from that of the firm's. He encouraged them to share tables as well as discuss issues in telephone conversations with reviewers. He emphasized that current rules preclude our sending the reviews to the firm prior to the stated deadline. In answer to item 3, he said, that there would be no change in the current committee membership by the July meeting.

Dr. John Wikstrand then presented their reanalysis of the study in view of the subgroup analysis question. He showed their own reanalysis of the data arguing against the no effect in U.S. patients found by FDA statistician. Dr. Cui emphasized the importance of taking a close look at the trial outcome in US patients because of the purpose of the submission. He also pointed out the essential difference between his and the sponsor's analysis.

The discussion then turned on the possibility of whether the firm might want to consider going before the advisory committee after action on this particular application has been completed. The committee could discuss this application together with other applications that also raised issue of subgroup analysis. The firm thought that this might be something that they would consider.

The firm summarized by asserting their belief that the subgroup analysis effect is not legitimate and that they disagreed with conducting such an analysis.

Dr. Lipicky stated that the issues are still evolving, and encouraged the firm to continue to communicate with the reviewers.

/S/

Recorder:

/ Natalia A. Morgenstern
Chief, Project Management Staff

/S/

Chair:

Director, Division of Cardio-Renal Drug Products

cc: Orig NDA

HFD-110

HFD-110/ Attendees

HFD-110/Matthews

HFD-110/ PM

Drafted: 4/12/00; Final: asb/4/21/00

RD: M Gordon/4/19/00

C Duarte/4/21/00

L Cui/4/19/00

Memorandum

Date: 1 Feb. 2001

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation I

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Cc: Raymond Lipicky, M.D., Dir., DCRDP (HFD-110)
Albert DeFelice, Ph.D., TL Pharm./Tox., DCRDP (HFD-110)

Subject: NDA 19-962, S-013
TOPROL-XL® Extended Release Tablets (metoprolol succinate)
Review of Pharm./Tox. Labeling

I. Materials Included in Review

1. Pharm./Tox. TL Review of NDA 19-962, S-013, dated 1 Feb. 2000, written by Albert DeFelice, Ph.D.
2. NDA 19-962, S013 Approval Package (19 Jan. 2001) with Draft Product Labeling (20 Dec. 2000)

II. Comments related to the Draft Product Label

A) Under the headings of "Carcinogenesis, Mutagenesis and Impairment of Fertility", "Pregnancy" and "Labor and Delivery" it is recommended that:

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B) Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:

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C) Under the heading of "Pregnancy" it is recommended that:

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III. Summary

A review of the action package for NDA 19-962, S013, TOPROL-XL® Extended Release Tablets, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for potential approval in a chronic use indication. The proposed product label, with possible revision as suggested in the preceding section of this memorandum, adequately reflects the non-clinical safety data for this product.

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 2/6/01 10:53:24 AM
From: Albert Defelice (DEFELICE)
Subject:

Dave: Thank you for the review of the pre-clinical labelling for Toprol XL (extended release metoprolol: NDA 19-962, S-013. The revisions you suggested are specified in your memo to Dr R. Temple of 2/1/01. I received this memo on 2/5/01 shortly before Dr. Temple's approval of this formulation/efficacy supplement. Ms Zelda McDonald and I met briefly with RT prior to his sign-off. He did not indicate the need to immediately upgrade the pre-clinical labelling for approval. I believe he was aware, as you are, that the pre-clinical labelling already incorporated my own revisions per Dr. DeGeorge's recommendations of 6/29/00. However, RT indicated that future upgrade of the labelling should/would be for all off-patent marketed metoprolol products, not just the XL formulation. At such time, your recommendations will need to be re-visited, and - together with any others from Dr. DeGeorge, myself or Dr. Resnick - addressed. Prior to, this I would suggest Joe DeGeorge, you, and other of Joe's deputies discuss format and "boiler plate" of typical labelling categories; as we discussed, and your suggestions for revision imply, this is a moving /evolving target.

Redacted

4

pages of trade

secret and/or

confidential

commercial

information