CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-956

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT CERTIFICATION

Paragraph I Certification

In accordance with the Federal Food, Drug, and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) application for NDA 21-956 for TRADENAME (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets, 25/12.5, 50/12.5 and 100/12.5 mg.

AstraZeneca LP (AstraZeneca) hereby certifies that, in its opinion and to the best of its knowledge, patent information has not been submitted to the FDA. This certification is made in accordance with Section 505(b)(2)(A)(i) of the FD&C Act and pursuant to 21 CFR 314.50(i)(1)(i)(A)(1).

Paula R. Clark
Regulatory Affairs Director

APPEARS THIS WAY
ON ORIGINAL

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
NDA 21-956

NAME OF APPLICANT / NDA HOLDER
AstraZeneca LP

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To be determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
metoprolol succinate and hydrochlorothiazide	50 mg (metoprolol succinate Extended Release)/12.5 mg (hydrochlorothiazide); 25 mg/12.5mg; 25 mg /6.25 mg; 100mg/12.5 mg

DOSAGE FORM
Tablets, extended release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,927,640	5/22/1990	5/22/2007

d. Name of Patent Owner
Aktiebolaget Hassle

Address *(of Patent Owner)*
SE-431 83

City/State
Mölndal, Sweden

ZIP Code
SE-431 83

FAX Number *(if available)*

Telephone Number
01146 31 7761000

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Vice President, General Counsel & Compliance Officer
AstraZeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code
19803

FAX Number *(if available)*

Telephone Number
(800) 456-3669

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No

4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

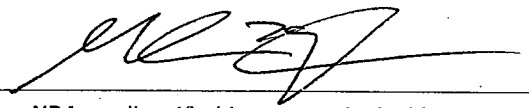
5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	10/10/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Glenn M Engelmann, Vice President, General Counsel & Compliance Officer	
Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3244
FAX Number *(if available)* (302) 886-1578	E-Mail Address *(if available)* glenn.engelmann@astrazeneca.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
NDA 21-956

NAME OF APPLICANT / NDA HOLDER
AstraZeneca LP

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To be determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
metoprolol succinate and hydrochlorothiazide	50 mg (metoprolol succinate Extended Release)/12.5 mg (hydrochlorothiazide); 25 mg/12.5mg; 25 mg /6.25 mg; 100mg/12.5 mg

DOSAGE FORM
Tablets, extended release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,001,161	3/19/1991	9/18/2007

d. Name of Patent Owner
AstraZeneca LP

Address *(of Patent Owner)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code	FAX Number *(if available)*
19803	
Telephone Number	**E-Mail Address *(if available)***
(800) 456-3669	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Vice President, General Counsel & Compliance Officer
AstraZeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code	FAX Number *(if available)*
19803	
Telephone Number	**E-Mail Address *(if available)***
(800) 456-3669	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*

Date Signed: 10/10/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Glenn M Engelmann, Vice President, General Counsel & Compliance Officer

Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3244
FAX Number *(if available)* (302) 886-1578	E-Mail Address *(if available)* glenn.engelmann@astrazeneca.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
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NDA NUMBER
NDA 21-956

NAME OF APPLICANT / NDA HOLDER
AstraZeneca LP

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To be determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
metoprolol succinate and hydrochlorothiazide	50 mg (metoprolol succinate Extended Release)/12.5 mg (hydrochlorothiazide); 25 mg/12.5mg; 25 mg /6.25 mg; 100mg/12.5 mg

DOSAGE FORM
Tablets, extended release

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,081,154	1/14/1992	9/18/2007

d. Name of Patent Owner
AstraZeneca LP

Address *(of Patent Owner)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code	FAX Number *(if available)*
19803	
Telephone Number	**E-Mail Address *(if available)***
(800) 456-3669	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Vice President, General Counsel & Compliance Officer
AstraZeneca Pharmaceuticals LP

Address *(of agent or representative named in 1.e.)*
1800 Concord Pike

City/State
Wilmington, DE

ZIP Code	FAX Number *(if available)*
19803	
Telephone Number	**E-Mail Address *(if available)***
(800) 456-3669	

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No*

* Certain claims may cover at least one additional polymorph in addition to claiming the drug substance of the pending NDA, amendment or supplement, but the patent is not being listed on that basis.

2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

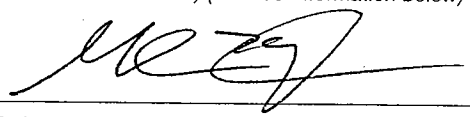
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	10/10/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Glenn M Engelmann, Vice President, General Counsel & Compliance Officer	
Address 1800 Concord Pike	City/State Wilmington, DE
ZIP Code 19803	Telephone Number (302) 886-3244
FAX Number *(if available)* (302) 886-1578	E-Mail Address *(if available)* glenn.engelmann@astrazeneca.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY FOR NDA # __21-956__ SUPPL #__N/A

Trade Name _____Dutoprol™_____ Generic Name metoprolol succinate extended-release/hydrochlorothiazide 25/12.5, 50/12.5 and 100/12.5 mg Tablets ____

Applicant Name __AstraZeneca LP___ HFD # _110___

Approval Date If Known August 28, 2006

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 /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

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

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? **5 YEARS**

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_**X**__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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. **N/A**

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# _____

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 /_X__/ NO /___/

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

NDA# __19-962___ **Toprol XL(metoprolol succinate ER)**

NDA# __11-835_ **Hydrochlorothiazide**

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 /_**X**__/ NO/_

(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:
Study #324

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 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

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 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

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"):

Study #324__

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

IND # 67,095 YES /_**X**__/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(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? **N/A**

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 /_**X**__/

If yes, explain: _____

_____

Signature Date: August 16, 2006
Title:Alisea Sermon, Pharm.D.
Regulatory Health Project Manager, HFD-110
(301) 796-1144

Signature of Office Date: August 16, 2005
Norman Stockbridge, M.D., Ph.D.
Division Director, HFD-110
Division of Cardio-Renal Drug Products

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-610 Mary Ann Holovac

AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19850-5437

TRADENAME (metoprolol succinate extended release and hydrochlorothiazide) Tablets
NDA 21-956

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

EXCLUSIVITY INFORMATION

Applicant claims an exclusivity period of five years from the date of approval of this New Drug Application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act which contains any active moiety in TRADENAME (to be determined) (metoprolol succinate extended release and hydrochlorothiazide) Tablets, the drug product for which Applicant is seeking approval.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-956 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: October 28, 2006 **Action Date:** August 28, 2006

HFD-110 **Trade and generic names/dosage form:** Dutoprol™ (metoprolol succinate extended-release/hctz) 25/12.5, 50/12.5 and 100/12.5 mg Tablets

Applicant: AstraZeneca LP **Therapeutic Class:** Beta Blockers

Indication(s) previously approved: Hypertension

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

- X **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ___Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
  Too few children with disease to study
- ☐ **There are safety concerns**
- X **Other: It does not represent a meaningful therapeutic benefit over existing treatment; each of its components of the combination is individually available; fixed dose combination therapy is not recommended from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** <6 years	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** <6 years	**Tanner Stage**_____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population

- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Alisea Sermon, Pharm.D.
Regulatory Project Manager
cc: NDA 21-956

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.(revised 12-22-03)

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

/s/

Denise Hinton
8/24/2006 04:01:49 PM
for Alisea Sermon

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,095

AstraZeneca LP
Attention: Ms. Cindy M. Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Please refer to your submission dated July 28, 2005, requesting a waiver for pediatric studies for ——— (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets.

We have reviewed the submission and agree that a waiver is justified for ——— (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets for the treatment of hypertension for the entire pediatric population because:

- it does not represent a meaningful therapeutic benefit over existing treatment
- it is unlikely to be used in a substantial number of pediatric patients
- each of the components of the combination is individually available
- fixed dose combination therapy is not recommended from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
301-594-5313

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
8/16/2005 08:33:33 AM

ITEM 16 DEBARMENT CERTIFICATION

Re: NDA 21-956

Metoprolol succinate extended release and hydrochlorothiazide Tablets

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

NDA 21-956

Dutoprol™
(metoprolol succinate extended-release/hctz) 25/12.5, 50/12.5 and 100/12.5 mg Tablets
AstraZeneca LP

The Financial Disclosure information was reviewed by Dr. A. Olufemi Williams. See pages 69 and 70 of his review dated May 31, 2006.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.
Toprol-XL
D4026C00006

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 REPORT(S)	

☐ (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	TITLE
Anthony F. Rogers	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca LP	
SIGNATURE: Anthony Rogers	DATE: 7/26/05

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

NDA 21-956
RHPM Review

RHPM Overview of NDA 21-956
Dutoprol™ (metoprolol succinate extended release/hydrochlorothiazide)
25/12.5 50/12.5 and 100/12.5 mg Tablets
August 16, 2006

Sponsor:	AstraZeneca
Receipt Date:	October 28, 2006
User Fee Goal Date:	August 28, 2006
AP Letter Issued:	

Background:
This new drug application provides for the submission of clinical studies to support an indication for the management of hypertension.

Medical
In his review dated July 16, 2006, Dr. Akinwole Williams recommended an approval of the combination fixed dose drug for the treatment of essential hypertension. The doses recommended include 100/6.25 mg; 100/12.5 mg and 100/25 mg. The fixed combination tablets planned for clinical use in the US include 3 tablet strengths: 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg. The 100/12.5 mg tablet is scored and is divisible to 50/6.25 mg.

Pharmacology Review
In his review dated July 7, 2006, Dr. Xavier Joseph recommended an approvable action for the combination product. He proposed changes under the **PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility*** **and *Pregnancy* subsections**. He stated that there are no approvability issues for the Metoprolol Succinate Extended Release/HCTZ combination product from the nonclinical toxicity testing program perspective.

Biopharmaceutical Review
In her review dated, August 14, 2006, Dr. Lydia Velazquez concluded that blood pressure differences between the two formulations were not statistically significant indicating no difference in clinical effect between the two drugs with regards to blood lowering effects. Standing heart rate 24 hours post dose was reduced significantly with the new combination; which may be due to the higher metoprolol plasma concentrations (24 hours post dose) with the new CR formulation resulting in a more sustained beta1-blockade at the end of the dosing interval. However, since assay methodology validation could not be verified, claims regarding formulation superiority can not be made.

HCTZ and Metoprolol pharmacokinetics were similar and demonstrated to be bioequivalent in both formulations. No formulation by food effect was detected in either formulation.

Statistical Review
In her review dated, May 19, 2006 Dr. Ququan Liu stated that Study 324 (ATTACH) has demonstrated that at least 1 Dutoprol-XL/HCT combination exceeds the blood pressure (BP) lowering effects of its individual components with regard to placebo-corrected change from

baseline to Week 8 in trough sitting diastolic blood pressure. The dose combination that performs better than its components was identified as Dutoprol-XL 100mg/HCT 12.5 mg. Support from Study S-902 is limited because of different study design, lacking consistent positive results and no multiplicity adjustment for multiple primary efficacy endpoints.

Chemistry Review
In his review dated, July 26, 2006 Dr. Haripda Sarker recommended an Approval regulatory action from a chemistry, manufacturing and controls standpoint because:
The applicant addressed all the deficiencies satisfactorily. In addition, he recommended for the following comments regarding shelf-life be included in the action letter:
"A shelf-life of twenty four months for the drug product will be granted based on stability data provided".

DSI
N/A

Pediatrics
The Division sent a pediatric waiver letter to the sponsor dated August 16, 2005.

Labeling
The sponsor submitted original labeling dated October 28, 2005. On August 9, 2006, the Division sent a draft electronic version of labeling revisions to the sponsor's original labeling proposal. On August 15, 2006, the sponsor revised the labeling and electronically resubmitted the changes for a teleconference scheduled on August 16, 2006.

Advisory Committee Meeting
No meeting held.

CSO Summary
To my knowledge, there are no issues that might prevent an approval on draft action on this NDA.

Alisea Sermon, Pharm.D.

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/s/

Alisea Sermon
9/27/2006 04:08:42 PM
CSO

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X Draft Labeling

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Office of Surveillance and Epidemiology

MEMO

To: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products, HFD-110

From: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

Date: July 27, 2006

Re: OSE Consult 06-0006 & 06-0006-1; Toprol XL/HCT, Dutoprol, and ——— (Metoprolol Succinate Extended-release and Hydrochlorothiazide); NDA 21-956.

This memorandum is written in response to the attached DMETS Proprietary Name Review conducted on Toprol XL/HCT, Dutoprol, and ——— or the Division of Cardiovascular and Renal Products (HFD-550). We have reviewed the safety evaluator's comments and we agree with the final conclusion of the unacceptability of the proposed names Toprol XL/HCT ——— However, we disagree with the final conclusion that the proposed name Dutoprol is unacceptable. The review found the proposed proprietary name unacceptable due to the potential for confusion with Ditropan and Ditropan XL. Specifically, the Safety Evaluator's review states:

> "Ditropan and Dutoprol contain eight letters and have a similar beginning ("Dit-" vs. "Dut-") with the letters "o" and "p" in the middle of the names. The endings of each name ("-an" vs. "-ol") may look similar if the upstroke of the "l" is not prominent when scripted. Additionally, the letter configuration of the names is similar, with upstrokes and downstrokes in similar positions.
>
> Ditropan and Dutoprol will be available in different strengths (5 mg and 10 mg vs. 25 mg/12.5 mg, 50 mg/12.5 mg and 100 mg/12.5 mg). However, the 12.5 mg hydrochlorothiazide strength of Dutoprol is consistent; thus, may be omitted from prescriptions. Although DMETS has no post-marketing evidence of this resulting in medication errors, currently practicing Expert Panelists indicated that this is seen in clinical practice. Thus, the potential exists for prescriptions for Dutoprol to appear as Dutoprol 25 mg [or 50 mg or 100 mg]. Specifically DMETS is concerned with the potential for confusion between the Ditropan 5 mg and Dutoprol 50 mg. The numerical strengths, 5 mg and 50 mg, may look similar if 5 mg is written with a trailing zero (5.0 mg), or 50 mg may look similar to 5 mg if the zero is not prominent and blends into the scripted "mg" unit. Thus, Ditropan 5 mg and Dutoprol 50 mg may look similar when scripted (see examples below).

> Furthermore, Ditropan and Dutoprol overlap in usual dosage/dosage form (1 tablet), and route of administration (oral). Although Ditropan and Dutoprol differ in indication for use (overactive bladder vs. hypertension), they may share an overlapping patient population. Despite the different dosing intervals of Ditropan and Dutoprol (BID-TID vs. QD), post-marketing surveillance has shown that the dosing frequency may not be enough to prompt practitioners as to what th product is if both names appear similar when scripted (e.g., Reminyl [dosed BID] and Amaryl [dosed QD]). Thus, r concerned with the potential for confusion between Ditropan and Dutoprol.

Additionally, Ditropan XL may look similar to Dutoprol when scripted. In addition to the aforementioned orthographic similarities between Ditropan and Dutoprol, the modifier "XL" may enhance the orthographic similarity between the two names because both names will end with an upstroke. Ditropan XL is available as 5 mg, 10 mg, and 15 mg tablets. If the hydrochlorothiazide strength from Dutoprol is omitted, prescriptions for Dutoprol may appear as Dutoprol 25 mg, Dutoprol 50 mg, or Dutoprol 100 mg. The numerical strengths of Ditropan XL 5 mg and 10 mg may look similar to Dutoprol 50 mg and 100 mg as previously described above. Thus, Ditropan XL 5 mg and Ditropan 10 mg may look similar to Dutoprol 50 mg and Dutoprol 100 mg when scripted. Furthermore, Ditropan XL and Dutoprol are both oral solid dosage forms that are dosed once daily. DMETS has concerns that the orthographic similarity (including the appearance of the upstroke ending), the similarity in numerical dose, and the overlapping dosage form (tablets) and frequency of administration (once daily) may increase the potential for confusion between Ditropan XL and Dutoprol.

Ditropan XL

Dutoprol

Additionally, since Toprol-XL is a commonly used drug product, the potential exists for practioners to write prescriptions for Dutoprol as Dutoprol XL, particularly since Dutoprol is an extended-release product dosed once daily. If Dutoprol is written as Dutoprol XL, this can be confused with Ditropan XL. A prescription for Dutoprol that designates only the metoprolol strength may be mistakenly written as Dutoprol XL 25 mg [50 mg or 100 mg]. For example, a prescription mistakenly written as Dutoprol XL 100 mg may be misinterpreted as Ditropan XL 10 mg if the numeric strength is poorly scripted. Although several contributing factors must occur for this type of error to happen, this is another scenario where there may be confusion between Ditropan XL and Dutoprol. Therefore, DMETS does not recommend the use of the proprietary name, Dutoprol.

Dutoprol XL 100mg

Ditropan XL 10mg

While we agree there are similarities between the names (Dutoprol vs. Ditropan and Ditropan XL) as identified by the Safety Evaluator, we believe that for an error to occur, three different misinterpretations must take place for one prescription order. First, the names must be misinterpreted. The beginnings of the names (Ditrop vs. Dutop) are almost identical in script but we believe that the endings of the names are somewhat distinguishable (an vs. rol) predominantly due to the upstroke letter at the end. We also agree that the modifier "XL" in Ditropan XL increases the look-alike similarity to Dutoprol given that they both share the ending of "L" and if the letter "X" is negligible in script.

Secondly, the hydrochlorothiazide strength must be omitted, leaving only the expression of the metoprolol strength on a prescription order for Dutoprol. Although, our practicing Safety Evaluators indicate that they have seen this occur in practice, our post-marketing searches did not reveal that this is a common practice by prescribers. Thus, prescriptions for Dutoprol will likely include both strengths of metoprolol and hydrochlorothiazide (i.e. 50 mg/12.5 mg) which will differentiate it from Ditropan and Ditropan XL.

Thirdly, the Safety Evaluator states that the metoprolol strength may be misinterpreted since the strengths of these products are numerically similar (50 mg and 5 mg). Finally, the Safety Evaluator states that Ditropan XL and Dutoprol share a once daily dosing schedule and that even though Ditropan and Dutoprol vary is dosing schedules, confusion will occur. While these concerns have been validated by post-marketing medication error cases, too many misinterpretation errors must occur before the wrong drug product is dispensed. For example, the prescription product name must be misinterpreted (Dutoprol vs. Ditropan or Ditropan XL), the strength of the hydrochlorothiazide must be omitted and then the strength of the metoprolol must be misinterpreted. Thus, our concerns for potential confusion are minimized because the three errors discussed above must occur sequentially for the wrong drug to be dispensed on a prescription order.

Additionally, the Safety Evaluator states that Dutoprol may be written as "Dutoprol XL" since it is an extended-release formulation of the commonly known drug product "Toprol XL." This could potentiate an error with Ditropan XL. Again, we believe that if this occurs, the prescriber would have to omit the strength of the hydrochlorothiazide component and the strength of the metoprolol component would have to be misinterpreted before the wrong drug product can be dispensed.

Based on the aforementioned reasons, we feel that the potential for name confusion between Dutoprol and Ditropan and Ditropan XL is minimal and that these two agents can safely co-exist in the marketplace. Therefore, DMETS has no objections to the use of the proposed name, Dutoprol. Please see the attached review for DMETS' label and labeling comments and for DDMAC comments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Alisea Sermon, PharmD
Division of Cardiovascular and Renal Products
Room# 4160, (301) 796-1144

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 5, 2006	67,095	21-956	Trade Name Review	December 28, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Toprol-XL/HCT	No	1	June 1, 2006

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: I will deliver the background information for this NDA.

PDUFA DATE: August 28, 2006
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 21-956
HFD-110/Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Alisea Sermon (301) 796-1144	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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

/s/

Alisea Sermon
1/5/2006 09:31:31 AM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: Jan. 5, 2006 **DATE OF DOCUMENT:** Dec. 28, 2005	**DESIRED COMPLETION DATE:** June 1, 2006 **PDUFA DATE:** Aug. 28, 2006	**OSE CONSULT #:** 06-0006 06-0006-1

TO: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products
HFD-110

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, BSN, MSEd, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Toprol-XL/HCT™** (primary name) **Dutoprol™** (alternate name) ——— (third name) (Metoprolol Succinate Extended-release and Hydrochlorothiazide) Tablets 25 mg/12.5 mg, 50 mg/12.5 mg, 100 mg/12.5 mg **NDA #:** 21-956	**SPONSOR:** AstraZeneca

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary names, Toprol-XL/HCT, Dutoprol or ——— Additionally, DMETS strongly urges the sponsor to exercise prudence in packaging, labeling, and advertising this product in order to prevent medication errors between the new combination product and the currently marketed Toprol-XL. DMETS also recommends an educational campaign to raise the awareness of health care providers and patients of the differences between the two products.

2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary names Toprol-XL/HCT, Dutoprol and ——— acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-5038.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 8, 2006

NDA#: 21-956

NAME OF DRUG: **Toprol-XL/HCT** (primary name)
Dutoprol (alternate name)
[redacted] third name)
(Metoprolol Succinate Extended-release and Hydrochlorothiazide) Tablets
25 mg/12.5 mg, 50 mg/12.5 mg, and 100 mg/12.5 mg

NDA HOLDER: AstraZeneca

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-110) for assessment of the proprietary names, "Toprol-XL/HCT", "Dutoprol", and [redacted] egarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

The Sponsor has included a proprietary name safety assessment from the [redacted] for the proprietary names Toprol-XL/HCT, Dutoprol, and [redacted] for review and comment.

PRODUCT INFORMATION

Toprol-XL/HCT/Dutoprol/ [redacted] is a combination tablet containing extended-release metoprolol succinate and hydrochlorothiazide (HCTZ). Toprol-XL/HCT/Dutoprol [redacted] indicated for the treatment of hypertension and will be available as 25 mg/12.5 mg, 50 mg/12.5 mg, and 100 mg/12.5 mg tablets to be dosed once daily. Dosing must be individualized considering baseline and target blood pressure as well as experience with individual agents. Patients usually do not require doses in excess of 50 mg hydrochlorothiazide daily when used concomitantly with other antihypertensive agents. Metoprolol succinate extended-release doses greater than 400 mg have not been studied. The product will be supplied in bottles of 100 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Toprol-XL/HCT/Dutoprol/ [redacted]) a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA).
[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Toprol-XL/HCT, Dutoprol, and ——— Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Toprol-XL/HCT, Dutoprol, and ———acceptable from a promotional perspective.

2. The Expert Panel identified four names that were thought to have the potential for confusion with Toprol-XL/HCT. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

3. The Expert Panel identified three names that were thought to have the potential for confusion with Dutoprol. These products are listed in Table 2 (see page 4), along with the dosage forms available and usual dosage.

4. The Expert Panel identified four names that were thought to have the potential for confusion with ——— hese products are listed in Table 3 (see pages 4 & 5), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names for Toprol-XL/HCT Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Toprol-XL/HCT	Metoprolol Succinate and Hydrochlorothiazide Extended-release Tablets: 25 mg/12.5 mg, 50 mg/12.5 mg, 100 mg/12.5 mg	Take one tablet by mouth once daily	
Toprol-XL	Metoprolol Succinate Extended-release Tablets: 25 mg, 50 mg, 100mg, and 200 mg	HTN: 50 mg -100 mg QD. Angina pectoris: 100 mg QD. CHF: 12.5 mg -200 mg QD.	LA/SA
Lopressor HCT	Metoprolol Tartrate and Hydrochlorothiazide Tablets: 50 mg/25 mg, 100 mg/25 mg, and 100 mg/50 mg	Dosage should be determined by individual titration. Hydrochlorothiazide is usually given at a dosage of 25 mg – 100 mg/day. The usual initial dosage of Lopressor is 100 mg daily in single or divided doses. Dosage may titrated up to 450 mg/day. Tablets of 50/25: 2 tablets per day in single or divided doses. Tablets of 100/25: 1-2 tablets per day in single or divided doses. Tablets of 100/50: 1 tablet per day in single or divided doses.	LA/SA

Product Name	Dosage form(s) / Established name	Usual adult dose*	Other**
Toprol-XL/HCT	Metoprolol Succinate and Hydrochlorothiazide Extended-release Tablets 25 mg/12.5 mg, 50 mg/12.5 mg, 100 mg/12.5 mg	Take one tablet by mouth once daily.	
Topamax	Topiramate Tablets: 25 mg, 50 mg, 100 mg, and 200 mg Capsule, sprinkle: 15 mg, 25 mg	Partial seizures: 200 to 400 mg/day in 2 divided doses. Tonic-clonic seizures: 400 mg/day in 2 divided doses. Migraine prophylaxis: 100 mg/day in 2 divided doses.	LA/SA
Tegretol XR	Carbamazepine Extended-release Tablets:100 mg, 200 mg, and 400 mg	200 mg BID not to exceed 1200 mg/day.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

Table 2: Potential Sound-Alike/Look-Alike Names for Dutoprol Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Dutoprol	Metoprolol Succinate and Hydrochlorothiazide Extended-release Tablets 25 mg/12.5 mg, 50 mg/12.5 mg, 100 mg/12.5 mg	Take one tablet by mouth once daily.	
Ditropan Ditropan XL	Oxybutynin Chloride Tablets: 5 mg Oral Syrup: 5 mg/5 mL Extended-release tablets: 5 mg, 10 mg, 15 mg	Tablets: 5 mg BID-TID. Syrup: 1 teaspoon BID-TID. Extended-release tablets: 5 mg once daily up to 20 mg/day.	LA
Detrol Detrol LA	Tolterodine Tartrate Tablets: 1 mg and 2 mg Extended-release capsules: 2 mg and 4 mg	Tablets: 2 mg BID. Extended-release tablets: 4 mg once daily.	LA/SA
Disophrol Disophrol Chronotabs	Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Tablets: 2 mg/60 mg Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Extended-release Tablets: 6 mg/120 mg	Immediate Release: Take one tablet every four to six hours, not to exceed four doses per day. Extended Release: Take one tablet every twelve hours.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

Table 3: Potential Sound-Alike/Look-Alike Names for [redacted] Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
[redacted]	Metoprolol Succinate and Hydrochlorothiazide Extended-release Tablets 25 mg/12.5 mg, 50 mg/12.5 mg, 100 mg/12.5 mg	Take one tablet by mouth once daily.	
Prinivil Zestril Prinzide Zestoretic	Lisinopril Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg Lisinopril and Hydrochlorothiazide Tablets:10 mg/12.5 mg, 20 mg/12.5 mg, and 20 mg/25 mg	Hypertension: Initial dose: 10 mg once daily. Usual dosage range: 20 mg to 40 mg once daily. Heart failure: 5 mg to 40 mg once daily. Acute MI: 5 mg after 24 hours, 10 mg after 48 hours, and then 10 mg once daily.	LA
Bets-Sitosterol	Dietary Supplement		LA/SA
Zebeta	Bisoprolol Fumarate Tablets: 5 mg and 10 mg	Take 5 mg to 20 mg once daily.	LA/SA

Dutoprol

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: Dutoprol 25mg/12.5mg 1 tab daily	Dutoprol 25 mg/12.5 mg Dispense #90 Take one by mouth once daily
Outpatient RX: Dutoprol 25mg/12.5mg #90 1 tab (1)	

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX: [redacted] 50 mg/12.5 mg 1 tablet daily	[redacted] 50 mg/12.5 mg Dispense #90 Take one by mouth once daily
Outpatient RX: [redacted] 50mg/12.5mg #90 1 tablet daily	

2. Results for Toprol-XL/HCT:

[redacted]

3. Results for Dutoprol:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed US product. See Appendix B for the complete listing of interpretations from the verbal and written studies.

4. Results for [redacted]

[redacted]

5 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

2. **Dutoprol**

In reviewing the proprietary name, Dutoprol, the primary concerns relating to look-alike and sound-alike confusion with Dutoprol are Ditropan, Ditropan XL, Detrol, and Disophrol. Although Disophrol was identified as a potential look-alike and sound-alike medication to Dutoprol, DMETS telephoned the sponsor, Schering-Plough, who stated that this over-the-counter drug product is no longer marketed. Furthermore, a generic formulation is not available. Thus, DMETS will not discuss this name further.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Dutoprol.

a. Ditropan was identified as a name with similar appearance to the proposed name, Dutoprol. Ditropan is available in an immediate-release and extended-release formuation. The immediate-release formulation is indicated for the relief of symptoms of bladder instability associated with voiding with patients with uninhibited neurogenic or reflex neurogenic bladder. The extended-release formulation (Ditropan XL) is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Ditropan and Dutoprol contain eight letters and have a similar beginning ("Dit-" vs. "Dut-") with the letters "o" and "p" in the middle of the names. The endings of each name ("-an" vs. "-ol") may look similar if the upstroke of the "l" is not prominent when scripted. Additionally, the letter configuration of the names is similar, with upstrokes and downstrokes in similar positions.

   Ditropan and Dutoprol will be available in different strengths (5 mg and 10 mg vs. 25 mg/12.5 mg, 50 mg/12.5 mg and 100 mg/12.5 mg). However, the 12.5 mg hydrochlorothiazide strength of Dutoprol is consistent; thus, may be omitted from prescriptions. Although DMETS has no post-marketing evidence of this resulting in medication errors, currently practicing Expert Panelists indicated that this is seen in clinical practice. Thus, the potential exists for prescriptions for Dutoprol to appear as Dutoprol 25 mg [or 50 mg or 100 mg]. Specifically DMETS is concerned with the potential for confusion between the Ditropan 5 mg and Dutoprol 50 mg.

   The numerical strengths, 5 mg and 50 mg, may look similar if 5 mg is written with a trailing zero (5.0 mg), or 50 mg may look similar to 5 mg if the zero is not prominent and blends into the scripted "mg" unit. Thus, Ditropan 5 mg and Dutoprol 50 mg may look similar when scripted (see examples below).

   Furthermore, Ditropan and Dutoprol overlap in usual dosage/dosage form (1 tablet), and route of administration (oral). Although Ditropan and Dutoprol differ in indication for use (overactive bladder vs. hypertension), they may share an overlapping patient population. Despite the different dosing intervals of Ditropan and Dutoprol (BID-TID vs. QD), post-marketing surveillance has shown that the dosing frequency may not be enough to prompt practitioners as to what the product is if both names appear similar when scripted (e.g., Reminyl [dosed BID] and Amaryl [dosed QD]). Thus, DMETS is concerned with the potential for confusion between Ditropan and Dutoprol.

Additionally, Ditropan XL may look similar to Dutoprol when scripted. In addition to the aforementioned orthographic similarities between Ditropan and Dutoprol, the modifier "XL" may enhance the orthographic similarity between the two names because both names will end with an upstroke. Ditropan XL is available as 5 mg, 10 mg, and 15 mg tablets. If the hydrochlorothiazide strength from Dutoprol is omitted, prescriptions for Dutoprol may appear as Dutoprol 25 mg, Dutoprol 50 mg, or Dutoprol 100 mg. The numerical strengths of Ditropan XL 5 mg and 10 mg may look similar to Dutoprol 50 mg and 100 mg as previously described above. Thus, Ditropan XL 5 mg and Ditropan 10 mg may look similar to Dutoprol 50 mg and Dutoprol 100 mg when scripted. Furthermore, Ditropan XL and Dutoprol are both oral solid dosage forms that are dosed once daily. DMETS has concerns that the orthographic similarity (including the appearance of the upstroke ending), the similarity in numerical dose, and the overlapping dosage form (tablets) and frequency of administration (once daily) may increase the potential for confusion between Ditropan XL and Dutoprol.

Ditropan XL

Dutoprol

Additionally, since Toprol-XL is a commonly used drug product, the potential exists for practioners to write prescriptions for Dutoprol as Dutoprol XL, particularly since Dutoprol is an extended-release product dosed once daily. If Dutoprol is written as Dutoprol XL, this can be confused with Ditropan XL. A prescription for Dutoprol that designates only the metoprolol strength may be mistakenly written as Dutoprol XL 25 mg [50 mg or 100 mg]. For example, a prescription mistakenly written as Dutoprol XL 100 mg may be misinterpreted as Ditropan XL 10 mg if the numeric strength is poorly scripted. Although several contributing factors must occur for this type of error to happen, this is another scenario where there may be confusion between Ditropan XL and Dutoprol. Therefore, DMETS does not recommend the use of the proprietary name, Dutoprol.

Dutoprol XL 10mg

Ditropan XL 10mg

b. Detrol was identified as a name with similar appearance to the proposed name, Dutoprol. Detrol is indicated for the treatment of overactive bladder. The beginning of Detrol and Dutoprol may look similar when scripted ("Det-" vs. "Dut-"). The names also share the same ending ("-rol"). However, Detrol and Dutoprol differ in length (6 letters vs. 8 letters), which provides a noticeable difference when scripted. Also the downstroke of the letter "p" helps to differentiate the middle of the names. Both drug products share overlapping routes of administration (oral) and usual dose/dosage form (1 tablet/1 capsule). However, differentiating product characteristics between Detrol and Dutoprol include strength (1 mg and 2 mg vs. 25 mg/12.5 mg, 50 mg/12.5 mg, and 100 mg/12.5 mg), indication for use (overactive bladder vs. hypertension), and dosing frequency (twice daily vs. once daily). Overall, the lack of convincing orthographic similarities and the differentiating product characteristics minimize the potential for confusion between Detrol and Dutoprol.

Detrol

Dutoprol

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2. Dutoprol

— identified the following names as having the potential for confusion with Dutoprol: Butorphanol, Detrol, Disophrol, Ditropan, Donnatal, Dulcolax, Duoneb, Duract, Duragesic, Duraphyl, Glucotrol, Metoprolol, Toprol, Toprol-XL, and Yutopar —— concludes that their analysis gives positive support to the use of the name Dutoprol.

Both the DMETS and — valuations identified the existing names, Disophrol, Detrol, and Ditropan as having potential confusion with Dutoprol. Additionally, DMETS identified Ditropan XL as having potential confusion with Dutoprol. DMETS discussed these names in section IID2 of this review. We concur that Detrol, Disophrol, and Dutoprol may co-exist in the marketplace; however, do not agree that Ditropan, Ditropan XL and Dutoprol can co-exist in the marketplace due to orthographic similarities and overlapping product characteristics (see section IID2a). DMETS believes that the remaining names identified by — can co-exist in the marketplace with Dutoprol.

3. —

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Toprol-XL/HCT, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENT

We note that the Description section of the package insert and the "Each tablet contains..." statement on the container label lists a metoprolol tartrate equivalent statement (e.g., Tradename 25/12.5 contains 23.75 mg of metoprolol succinate extended release equivalent to 25 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide). However, the "Dosing and Administration" section states that the drug is dosed on metoprolol succinate. This is confusing especially since there are products currently marketed that contain metoprolol tartrate and

hydrochlorothiazide (see section IID1(c) of this review). Please explain the rationale for including the equivalent tartrate dose.

B. CONTAINER LABEL (Toprol-XL/HCT and Dutoprol: 25 mg/12.5 mg, 50 mg/12.5 mg and 100 mg/12.5 mg)

1. We note the dosage form is not included with the established name. Revise the label to include the dosage form as noted in comment A1.

2. The product strength only indicates the milligram units for the hydrochlorothiazide portion of the strength (e.g., 25*/12.5 mg, 50*/12.5 mg, 100*/12.5 mg). In order to avoid the metoprolol succinate extended-release strength being confused as a quantity, revise the product strength so that the milligrams units are indicated for both active ingredients. For example:

   25 mg*/12.5 mg 50 mg*/12.5 mg 100 mg*/12.5 mg

3. Although the background color of the container labels are different colors, each strength is presented using the same color. In order to avoid confusion, ensure the product strengths are clearly differentiated by contrasting colors, boxing or some other means.

4. Decrease the font size or further relocate the net quantity further away from the proprietary name, in order to minimize the likelihood of "100" being confused as the product strength. This is especially important since this drug will be available Toprol-XL/HCT comes in a 100 mg/12.5 mg strength.

5. Decrease the size of the sponsor's name and logo as it appears almost as prominent as the proprietary name.

C. INSERT LABELING

1. See comment B2 and apply it throughout the labeling.

2. When the product strengths are written in succession in the "Clinical Trials" section, the quantifying unit is omitted (e.g., 25, 50, 100 and 200 mg). To avoid confusion with the product strengths, include the "mg" abbreviation after each number (e.g., 25 mg, 50 mg, 100 mg, and 200 mg).

3. The "Pharmacokinetics" section contains a numeral that uses a terminal zero (2.0 hours). Remove the terminal zero as 2.0 hours can be misinterpreted as 20 hours. Additionally, on June 14, 2006 , FDA launched a nationwide health professional education campaign aimed at the reducing the number of common but preventable sources of medication errors caused by the use of unclear medical abbreviations and warned against using abbreviations, trailing zeros, and dose designations that appear on the ISMP dangerous abbreviations list (see press release http://www.fda.gov/bbs/topics/NEWS/2006/NEW01390.html).

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Appendix B: Dutoprol Prescription Study Results

Written Inpatient	Written Outpatient	Verbal
Autoprel	Diltaprol	Detopral
Dritoprol	Dretoprol	Detoprol
Dutopriol	Dutanol	Detoprol
Dutopriol	Dutgnol	Ditoprol
Dutopriol	Dutgnot	Dutoprol
Dutopriol	Dutoproe	Dutoprol
Dutopriol	dutoprol	Dutoprol
Dutoprol	Dutoprol	DuToprol
Dutoprol	Dutoprol	Dutoprol
Dutoprol	Dutoprol	Dutoprol
Dutoprol	Dutoprol	Dutoprol
Dutoprol	Dutoprol	dutoprol
Dutoprol	Dutoprol	Dutoprol
Dutoprol	Dutoprol	Dutropla
Dutoprol	Dutoprol	Neutoprol or Newtoprol
Dutoprol	Dutoprol	
Dutoprol	Dutoprol	
Dutoprol	Dutoprol	
Dutoprol		
Dutroprol		

Comment from one participant in the inpatient written study: "Dutoprol- too similar to Ditropan".

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ISMP's List of *Error-Prone Abbreviations, Symbols and Dose Designations* (continued)

Dose Designations and Other Information	Intended Meaning	Misinterpretation	Correction
Drug name and dose run together, especially problematic for drug names ending in "l" (e.g., Inderal40 mg, Tegretol300 mg)	Inderal 40 mg Tegretol 300 mg	Mistaken as Inderal 140 mg Mistaken as Tegretol 1300 mg	Place adequate space between the drug name, dose, and unit of measure
Dose and dose unit of measure run together (e.g., 10mg, 100mL)	10 mg 100 mL	The "m" is sometimes mistaken as a zero or two zeros, risking a 10- to 100-fold overdose	Place adequate space between the dose and unit of measure
Abbreviations such as mg, mL with a period after them (e.g., 10.mg)	mg mL	The period is unnecessary and could be mistaken as the number 1 if written poorly	Use mg, mL, etc. without a terminal period
Large doses without comma or other method of separating digits (e.g., 10000 units, 100000 units)	100,000 units 1,000,000 units	100000 has been mistaken as 10,000 or 1,000,000; 1000000 has been mistaken as 100,000	Use commas for dosing units at or above 1,000, or use words such as 100 "thousand" or 1 "million" to improve readability

Drug Name Abbreviations	Intended Meaning	Misinterpretation	Correction
ARA-A	vidarabine	Mistaken as cytarabine (ARA C)	Use complete drug name
AZT	zidovudine (Retrovir)	Mistaken as azathioprine or aztreonam	Use complete drug name
CPZ	Compazine (prochlorperazine)	Mistaken as chlorpromazine	Use complete drug name
DPT	Demerol-Phenergan-Thorazine	Mistaken as diphtheria-pertussis-tetanus (vaccine)	Use complete drug name
DTO	Diluted tincture of opium, or deodorized tincture of opium (Paregoric)	Mistaken as tincture of opium	Use complete drug name
HCl	hydrochloric acid or hydrochloride	Mistaken as potassium chloride (The "H" is misinterpreted as "K")	Use complete drug name unless expressed as a salt of a drug
HCT	hydrocortisone	Mistaken as hydrochlorothiazide	Use complete drug name
HCTZ	hydrochlorothiazide	Mistaken as hydrocortisone (seen as HCT250 mg)	Use complete drug name
MgSO4**	magnesium sulfate	Mistaken as morphine sulfate	Use complete drug name
MS, MSO4**	morphine sulfate	Mistaken as magnesium sulfate	Use complete drug name
MTX	methotrexate	Mistaken as mitoxantrone	Use complete drug name
PCA	procainamide	Mistaken as patient controlled analgesia	Use complete drug name
PTU	propylthiouracil	Mistaken as mercaptopurine	Use complete drug name
T3	Tylenol with codeine No. 3	Mistaken as liothyronine	Use complete drug name
TAC	triamcinolone	Mistaken as tetracaine, Adrenalin, cocaine	Use complete drug name
TNK	TNKase	Mistaken as "TPA"	Use complete drug name
ZnSO4	zinc sulfate	Mistaken as morphine sulfate	Use complete drug name

Stemmed Drug Names	Intended Meaning	Misinterpretation	Correction
Nitro drip	nitroglycerin infusion	Mistaken as sodium nitroprusside infusion	Use complete drug name
Norflox	norfloxacin	Mistaken as Norflex	Use complete drug name
Vanc	intravenous vancomycin	Mistaken as Invanz	Use complete drug name

Symbols	Intended Meaning	Misinterpretation	Correction
ʒ	Dram	Symbol for dram mistaken as "3"	Use the metric system
ℿ	Minim	Symbol for minim mistaken as "mL"	
x3d	For three days	Mistaken as "3 doses"	Use "for three days"
> and <	Greater than and less than	Mistaken as opposite of intended; mistakenly use incorrect symbol; "< 10" mistaken as "40"	Use "greater than" or "less than"
/ (slash mark)	Separates two doses or indicates "per"	Mistaken as the number 1 (e.g., "25 units/10 units" misread as "25 units and 110" units)	Use "per" rather than a slash mark to separate doses
@	At	Mistaken as "2"	Use "at"
&	And	Mistaken as "2"	Use "and"
+	Plus or and	Mistaken as "4"	Use "and"
°	Hour	Mistaken as a zero (e.g., q2° seen as q 20)	Use "hr," "h," or "hour"

**These abbreviations are included on the JCAHO's "minimum list" of dangerous abbreviations, acronyms and symbols that must be included on an organization's "Do Not Use" list, effective January 1, 2004. Visit www.jcaho.org for more information about this JCAHO requirement.

Institute for Safe Medication Practices
www.ismp.org

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/s/

Felicia Duffy
7/28/2006 10:06:29 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/28/2006 11:36:06 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/28/2006 12:04:10 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/28/2006 12:12:08 PM
DRUG SAFETY OFFICE REVIEWER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-956**	Efficacy Supplement Type **N/A**	Supplement Number **N/A**	
Drug: **Dutoprol™ (metoprolol/HCTZ) 25/12.5, 50/12.5 and 100/12.5 mg Tablets**		Applicant: **AstraZeneca, Inc.**	
RPM: **Alisea Sermon, Pharm.D.**		HFD- **110**	Phone # **(301) 796-1144**

Application Type: ( ) 505(b)(1) (**X**) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (**X**) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): **Hydrochlorothizide** **Toprol XL**

❖ Application Classifications:	
Review priority	(**X**) Standard ( ) Priority
Chem class (NDAs only)	
Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**August 28, 2006**
❖ Special programs (indicate all that apply)	(**X**) None Subpart H ( ) 21 CFR 314.510 (accelerate approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
User Fee Information	
User Fee	(**X**) Paid UF ID number **3006264**
User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation () Other
User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
❖ Application Integrity Policy (AIP)	
Applicant is on the AIP	( ) Yes (**X**) No

This application is on the AIP	( ) Yes (**X**) No
Exception for review (Center Director's memo)	
OC clearance for approval	
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(**X**) Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(**X**) Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	**Patent 1 Certification** 21 CFR 314.50(i)(1)(*i*)(A) (**X**) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	(**X**) N/A (no paragraph IV certification) ( ) Verified ( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	( ) Yes ( ) No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	**No**
Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**September 27, 2006**

General Information	
❖ Actions	
Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
Most recent applicant-proposed labeling	**August 15, 2006**
Original applicant-proposed labeling	**October 28, 2005**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DMETS: July 28, 2006** **DDMAC: June 13, 2006**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**X**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
Applicant proposed	**October 28, 2006**
Reviews	**See DMETS AND CMC reviews**
Post-marketing commitments	
Agency request for post-marketing commitments	
Documentation of discussions and/or agreements relating to post-marketing commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	**ACK Letter- November 8, 2005, 2005** **Filing Letter- January 10, 2006** **Information Request Ltr- June 13, 2006** **Pediatric Waiver Letter- August 16, 2005**
Memoranda and Telecons	**N/A**
Minutes of Meetings	
EOP2 meeting (indicate date)	N/A
Pre-NDA meeting (indicate date)	**January 19, 2005**
Pre-Approval Safety Conference (indicate date; approvals only)	N/A
Other- **Type C**	**September 30, 3004**
Advisory Committee Meeting	
Date of Meeting	
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**July 16, 2006**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
Pediatric Page(separate page for each indication addressing status of all age groups)	
Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	**May 19, 2006**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**August 14, 2006**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	N/A
Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**July 26, 2006**
Environmental Assessment	Refer to CMC review
Categorical Exclusion *(indicate review date)*	**Refer to CMC review**
Review & FONSI *(indicate date of review)*	N/A
Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm Tox Information	
Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**July 7, 2006**
Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA 21-956
Metoprolol succinate ER/Hydrochlorothiazide

1. Does the application reference a listed drug (approved drug)? YES **X** NO

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): **Hydrochlorothiazide**

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO **X**

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO **X**

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO **X**

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES **X** NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES **X** NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO **X**

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s): **Lopressor HCT® (metoprolol tartrate immediate release/hydrochlorothiazide)**

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES **X** NO

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. **NO**

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **The proposed product is:**
Metoprolol Succinate Extended Release/Hydrochlorothiazide

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO **X**

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under YES ☐ NO **X**

21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO **X**

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO **X**

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

X 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the

Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES **X** NO ☐

  *If "**Yes**," what is the listed drug product(s)* ***Hydrochlorothiazide*** *and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug* **Pharmacology/Toxicology**
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES **X** NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A **X** YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO **X**

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Alisea Sermon
7/7/2006 10:14:26 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-956

INFORMATION REQUEST LETTER

AstraZeneca LP
Attention: Ms.Paula Clark
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Clark:

Please refer to your October 28, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metoprolol/Hydrochlorothiazide 25/12.5 mg, 50/12.5 mg and 100/12.5 mg Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Please provide revised HCT (hydrocholorothiazide) specifications showing the deletion of [redacted]) and [redacted]

Drug Product

2. Based on daily dose, the reporting threshold for impurities is 0.05% as per ICHQ3B. All impurities/degradants above reporting threshold should be reported in future. The actual results for individual impurities should be reported rather than <0.2% as reported in drug product batches (e.g. section P.5.4., Table 2 through Table 8).

3. Please include an asterisk mark on metoprolol strength representation in the carton/container labels of all dosage strengths (e.g. 50/12.5) and the note "Each tablet contains--------hydrochlorothiazide". Please refer to the strength representation on the labels of your metoprolol monotherapy product approved under NDA 19-962.

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
6/13/2006 03:45:33 PM

MEMORANDUM

To: Alisea Sermon, Project Manager
Division of Cardiovascular and Renal Products, HFD-110

From: Lisa Hubbard, R.Ph., Senior Regulatory Review Officer, DDMAC
Jialynn Wang, Pharm. D., Group Leader, DDMAC

Date: June 13, 2006

Re: Comments on draft labeling:
NDA 21-956
Metoprolol succinate/HCTZ ER

DDMAC has reviewed the proposed package insert for NDA 21-956 (Metoprolol succinate/HCTZ ER) and offers the following comments with regard to promotional considerations:

Clinical Trials:

The Clinical Trials section of the product labeling contains the following language, "Blood pressure declines were apparent within 2 weeks and were maintained thereafter. The blood pressure lowering 24 hours post dosing retained approximately 96% of the peak (6 hours post dosing) effect." Both statements may be used for promotional purposes. Please consider revising the language to state the specific duration of the blood pressure lowering effect (rather than, "maintained thereafter.") Please also consider including contextual language related to the relevance of maintaining 96% of the peak effect 6 hours post dosing or consider eliminating the language.

Precautions:

The Precautions section of the product labeling contains the following statement, "The precautions for the use of metoprolol succinate extended release/hydroclorothiazide are the same as for the individual agents." The statement is unnecessary and may be used for promotional purposes. Please consider eliminating the statement.

Information for Patients:

The Information for Patients section of the proposed product labeling **does not** include the following statement found in the Ziac labeling, "Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia, and bisoprolol fumarate should be used with caution." If a similar effect is possible with this combination product, please consider including a similar statement in the same section of the proposed product labeling. The absence of such a statement could be used as a promotional advantage by a firm.

Adverse Reactions:

The Adverse reactions section of the product labeling contains the following statement, "Overall, the incidence of adverse experiences reported with the combination was comparable to placebo." We note that similar language appears in the product labeling for other products (i.e., Diovan HCT). However, the statement is promotional in tone and has been used in other drug classes

for promotional purposes. Please note the statement does not appear in the product labeling for Toprol XL or Hydrodiuril. Please consider eliminating the statement.

Over dosage:

The Over dosage section of the metoprolol and hydrochlorothiazide label contains the statement, "If over dosage of metoprolol and hydrochlorothiazide is suspected, the patient should be observed closely". The same section in the Ziac label states, "Ziac should be discontinued." Please consider the need for similar recommendations between the two products. The difference described above may provide a promotional advantage to the firm.

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/s/

Lisa Hubbard
6/13/2006 09:57:02 AM
DDMAC REVIEWER

AstraZeneca

Date: APR 17 2006

Norman Stockbridge, MD, PhD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-12666

Re: NDA 21-956
TRADENAME (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets, 25/12.5 mg, 50/12.5 mg and 100/12.5 mg
General Correspondence:
REDESIGNATION OF ORIGINAL NDA TO 505(b)(2)

Dear Dr. Stockbridge:

Reference is made to the original New Drug Application (NDA) 21-956 for TRADENAME (metoprolol succinate and hydrochlorothiazide) Extended Release (ER) Tablets, submitted to the Division on October 28, 2006. Reference is also made to the telephone conversation between Ms. Alisea Sermon of the Division and Ms. Paula Clark of AstraZeneca on April 11, 2006. Ms. Sermon informed Ms. Clark during this conversation that Office Level Staff had reviewed this original NDA and a request has been to AstraZeneca to redesignate this NDA to a Type 505(b)(2) application.

NDA 21-956 is an application for a new chemical entity (NCE) for a combination of metoprolol succinate ER and hydrochlorothiazide in tablet strengths of 25/12.5 mg, 50/12.5 mg and 100/12.5 mg of metoprolol succinate ER and hydrochlorothiazide, respectively. The Division has determined this NDA to be 505(b)(2) application since pharmacology/toxicology data for the hydrochlorothiazide component has been supported by published literature.

1. NO
2-Blank
3.

In accordance with the Federal Food, Drug and Cosmetic Act (the Act), and 21 CFR 314.45, AstraZeneca LP is providing a revised Form FDA 356h, redesignating the original New Drug Application, NDA 21-956 for TRADENAME (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets, submitted on October 28, 2005 as 505(b)(2) submission.

This submission is being provided in the enclosed binder(s) and includes:

- A completed and signed Form FDA 356h
- The original signed Cover Letter
- Patent Certification

AstraZeneca LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437

Tel 302 886 3000
www.astrazeneca-us.com

This electronic submission is being provided on CD-ROM. The media containing the electronic items of the submission has been scanned using Symantec AntiVirus, Version 9.0.1.1100 (Corporate Edition), with a virus definition list dated 4/13/2006 rev. 7. No viruses were detected, and AstraZeneca certifies that the media is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Pat Patterson, Associate Director, at (302) 885-1539.

Sincerely,

Paula R Clark

Paula R. Clark, Director
Regulatory Affairs
Telephone: (302) 885-1492
Fax: (302) 886-2822

Enclosure

Technical Review Jacket: Alisea Sermon, Regulatory Health Project Manager, Division of Cardiovascular and Renal Products

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT AstraZeneca LP	DATE OF SUBMISSION APR 17 2006
TELEPHONE NO. *(Include Area Code)* (800) 456-3669	FACSIMILE (FAX) Number *(Include Area Code)* (302) 886-2822
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE:

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-956

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* metoprolol succinate extended release and hydrochlorothiazide	PROPRIETARY NAME *(trade name)* IF ANY To Be Determined

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Metoprolol succinate is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is C7H8ClN3O4S2.

CODE NAME *(if any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	25mg/12.5; 50 mg/12.5; 100 mg/12.5	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Hypertension

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Submission of Revised 356h Form and Patent Certification - Redesignation of New Drug Application as 505(b)(2)

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS: ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 67,095; IND; NDA 19-962; DMF:

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☒	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k) (1))
☒	17. Field copy certification (21 CFR 314.50 (l) (3))
☒	18. Use Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Submission of Revised 356h Form and Patent Certification - Redesignation of New Drug Application as 505(b)(2)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Paula R Clark	Paula Clark Regulatory Affairs Director	APR 17 2006

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1800 Concord Pike, P.O. Box 8355 Wilmington, DE 19803-8355	(302) 885-1492

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1226

Department of Health and Human Services
Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-956

AstraZeneca LP
Attention: Ms. Cindy M. Lancaster
1800 concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Please refer to your October 28, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metoprolol Succinate and Hydrochlorothiazide Extended Release 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 27, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please contact:

Alisea Sermon, PharmD
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Division Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
1/10/2006 07:54:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-956

NDA ACKNOWLEDGMENT

AstraZeneca LP
Attention: Ms. Cindy M. Lancaster
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: metoprolol succinate and hydrochlorothiazide 25mg/12.5, 50 mg/12.5, 100 mg/12.5 Extended Release Tablets

Review Priority Classification: Standard (S)

Date of Application: October 28, 2005

Date of Receipt: October 28, 2005

Our Reference Number: NDA 21-956

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 27, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 28, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products, Room 4160
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
11/8/2005 09:56:36 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

ASTRAZENECA LP
Cindy Lancaster
1800 Concord Pike P.O. Box 8355
Wilmington DE 19803-8355
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21956

2. TELEPHONE NUMBER
302-885-1348

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
To Be Determined (Metoprolol succinate extended release and hydrochlorothiazide tablets)

6. USER FEE I.D. NUMBER
PD3006264

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Paula R Clark for Cindy M. Lancaster	Director Regulatory Affairs	OCT 12 2005

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

AstraZeneca

Date: OCT 12 2005

US Food and Drug Administration (360909)
Mellon Client Service Center
Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

RE: NDA 21-956
Trade Name: To be Determined
(metoprolol succinate extended release and hydrochlorothiazide) Tablets
25 mg/12.5 mg; 50 mg/12.5 mg; 100 mg/12.5 mg
Prescription Drug User Fee Payment: User Fee I.D. No. PD3006264

Dear Madam/Sir:

In accordance with section 736 of the Federal Food, Drug and Cosmetic Act, AstraZeneca LP (AstraZeneca) is providing a Prescription User Fee payment for a NDA for the use of metoprolol succinate extended release and hydrochlorothiazide tablets, for the treatment of hypertension. The product strengths of metoprolol succinate extended release and hydrochlorothiazide respectively, are 25 mg/12.5 mg; 50 mg/12.5 mg; 100 mg/12.5 mg. Please note the trade name for this combination product is to be determined.

The User Fee payment is made in the amount of $767,400.00 and represents the total NDA application fee for fiscal year 2005. A copy of the User Fee Cover Sheet, Form FDA 3397, is enclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Paula Clark, Associate Director at 302-885-1492.

Sincerely,

Paula R Clark for

Cindy M. Lancaster, Director
Regulatory Affairs
Telephone: (302) 885-1348
Fax: (302) 886-2822

Enclosure

Form FDA 3397 – User Fee Cover Sheet
User Fee Check No. 1500069811

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

AZ0010 (6/00)

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

ASTRAZENECA LP
Cindy Lancaster
1800 Concord Pike P.O. Box 8355
Wilmington DE 19803-8355
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21956

2. TELEPHONE NUMBER
302-885-1348

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
To Be Determined (Metoprolol succinate extended release and hydrochlorothiazide tablets)

6. USER FEE I.D. NUMBER
PD3006264

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
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12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Barbara Ann Cindy M. Lancaster	Director Regulatory Affairs	OCT 12 2005

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

(IBE_PRMT_CLOSE_G) (Print Cover sheet)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	302-886-2822
Attention:	Ms. Cindy Lancaster
Company Name:	**AstraZeneca**
Phone:	**302-885-1348**
Subject:	**Meeting Minutes**
Date:	2/1/05
Pages including this sheet:	7
From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Meeting

Meeting Date:	January 19, 2005
IND:	67,095
Drug:	[redacted] (metoprolol succinate extended release and hydrochlorothiazide) Tablets
Sponsor:	AstraZeneca
Type of Meeting:	Pre-NDA
Classification:	B

FDA Participants

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Clinical, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Stuart Zimmerman, Ph.D.	Chemist, HFD-810
Nhi Beasley, Pharm.D.	Pharmacokineticist, HFD-860
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Xavier Joseph, Ph.D.	Pharmacologist, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

AstraZeneca Participants

Cindy Lancaster	Director, Regulatory Affairs
Paula Clark	Associate Director, Regulatory Affairs
James Hainer	Senior Director, Clinical Research
Maria Sunzel	Director, Clinical Pharmacology
Jennifer Sugg	Senior Statistical Scientist
Robert Timko	Director, Technical Regulatory Affairs
Inger Borjesson	Pharmaceutical Project Manager
Jo Ann Saye	Director, Preclinical Sciences

Background:
An End of Phase 2 meeting was held on January 24, 2003 to discuss the development of this combination product. The sponsor is developing [redacted] for the treatment of hypertension. The sponsor is planning on marketing this combination product in the following doses: 25-6.25, 25-12.5, 50-12.5, and 100-12.5 mg Tablets.

Meeting:
Questions
Labeling

1. Should the Toprol-XL combinations with HCT 6.25 mg prove superior to placebo and demonstrate an acceptable safety profile relative to high dose monotherapy, does the Agency concur that this would support an 'initial treatment' indication?

   Dr. Stockbridge began by inquiring what the sponsor's understanding was for deciding when a combination product should be labeled for initial treatment. The sponsor stated based on the End of Phase 2 meeting held with the Division in January 2003, they believed that if the low dose of the combination product worked as well or better than the high dose of the monotherapy and had an additional advantage, such as a superior safety profile, this would provide support for the combination product to be labeled for initial treatment. The sponsor also believed that if the results were not achievable with the individual components of the combination, this would be another scenario that would allow for labeling as initial treatment. Dr. Stockbridge inquired what argument the sponsor planned to use to support their request. The sponsor stated they looked at the approval of Ziac as a model. In that case, Ziac, at low doses, was shown to be more beneficial than the higher monotherapy doses and had other additional benefits. Dr. Stockbridge inquired if the sponsor believed they would be able to sustain such an argument with the data they have available. The sponsor stated that they believe the data shows that [redacted] at low doses (25-6.25, 50-6.25, 25-12.5, and 50-12.5 mg) has a greater effect than high doses (25 mg) of hydrochlorothiazide. Dr. Stockbridge noted that this argument is not very persuasive looking at the individual

cells and noting the p-values, ranging from approximately 0.2-0.7. Dr. Stockbridge inquired if the sponsor has developed a model to look at this data. The sponsor stated they did not.

Dr. Stockbridge agreed that the sponsor's best argument is that low doses of [redacted], may keep patients from having to take hydrochlorothiazide 25mg. However, it appears that in order to get the blood pressure reduction achieved with 25 mg hydrochlorothiazide, you would need 100 mg Toprol XL and 12.5 mg hydrochlorothiazide. Therefore, it would be hard to argue that this case is similar to that of Ziac.

Dr. Stockbridge believes in order to get a labeling claim for initial treatment, the data would need to show that the low dose of the combination product was more effective than the higher dose of both monotherapies and/or to gain a desirable blood pressure effect, the combination was clearly safer. Dr. Stockbridge believes the sponsor will have to present a persuasive argument why someone starting treatment should be initiated on two products simultaneously rather than one and titrated upward until it is maximized and then add additional therapies as needed. In the case of Ziac, the sponsor was able to show efficacy in the combination product at low doses that would not have been sensible to administer as monotherapies. The sponsor added that in their trials the hydrochlorothiazide arm outperformed their expectations, and that of the same arm in the Ziac development program.

The sponsor believes that there is an important safety issue to note with lower doses of hydrochlorothiazide. The sponsor showed a graph depicting dose-related changes in potassium and uric acid. Dr. Stockbridge agreed that this could be incorporated into their argument, but he believes this would provide further rationale for adding Toprol XL sooner to patients on hydrocholorothiazide. Dr. Stockbridge does not believe this would provide a rationale for labeling [redacted] for initial treatment.

Dr. Stockbridge believed the sponsor may be able to argue for labeling for initial treatment if they were able to show that it would be beneficial for patients requiring more aggressive initial therapy. In this scenario, patients who are far from goal and it is obvious to a physician that they will be unable to get to their goal with monotherapy alone would be started on the combination. Dr. Stockbridge stated that Hyzaar is currently labeled this way. However, in the case of Hyzaar, the sponsor supported this claim by conducting a specific trial which showed that these types of patients were identifiable and achieved and maintained their goal better with initiation of combination therapy over monotherapy. The labeling does not specifically mention the goals or instruct physicians on how to choose patients that would benefit from this treatment, but only describes the clinical trial. Dr. Stockbridge added that such a claim has not been included in any labeling without a trial to support it. Dr. Stockbridge was unsure if the sponsor would be able to extract this data from their trial and present a compelling argument for the Division to review.

In summary, Dr. Stockbridge believes that in order for the sponsor to gain a labeling claim for initial treatment, they would need to show that [redacted], at the low dose, is better than both high doses of the monotherapy or provide a compelling argument why being better than one monotherapy would be sufficient. In addition, the sponsor would need to have an additional advantage over monotherapy, such as a better safety profile. The sponsor inquired if they should reevaluate their safety findings in order to have a stronger argument of increased safety with the combination. Dr. Stockbridge believed their current approach is acceptable, but he added that he wouldn't discourage the sponsor from doing further analyses on their safety data, uncorrected for multiplicity.

Clinical/Statistical

2. The Clinical study report for S-902 used WHOAED for AE coding. AstraZeneca plans to include an appendix to the study report that includes the original dictionary terminology (WHOAED) and the corresponding MedDRA terminology but does not plan to re-code individual patient adverse event data. Does the Agency concur that this is acceptable?

Dr. Stockbridge inquired about more details from this trial, as it appears to be very small and not add much value. The sponsor stated they are including this trial for full disclosure. It is an old trial performed approximately 13 years ago with 48 patients. The trial looked only at the 100-12.5 mg dose and looked at a population who was not controlled with diuretic therapy. In this case, the Agency agreed.

3. As part of the clinical study report, AstraZeneca will provide individual patient data for this 48 patient study, categorized into clinically meaningful listings and proposes that this can serve in lieu of datasets and individual patient data profiles within Item 11 dataset. Does the Agency concur with this proposal to only include these listings in the clinical study report?

   The sponsor clarified that they have the listings, but not by individual patients. Instead they are grouped by types of data. Dr. Stockbridge stated that since it appears this is not an important trial, this is acceptable. However, if it is believed that critical pieces are needed for review, datasets will need to be submitted and the formatting will not be as important.

4. Based on study 324, the sponsor concludes that each component (hydrochlorothiazide and metoprolol succinate extended release) contributes to the combination antihypertensive effect and that this finding meets the regulatory criterion for an effective combination product. Does the Agency agree?
   Based on study 324, the sponsor concludes that the low dose combination (hydrochlorothiazide 6.25 plus metoprolol succinate extended release 25 mg) is an effective antihypertensive agent and can be recommended as at least one starting dose. Does the Agency agree?
   The sponsor further asserts that metoprolol succinate extended release in combination with low doses of hydrochlorothiazide including hydrochlorothiazide 6.25 mg is a clinically preferable treatment to higher dose hydrochlorothiazide monotherapy and, as such, can be recommended as an initial treatment for hypertension. Does the Agency agree?

   Dr. Stockbridge began by stating the issue of initial treatment has already been discussed. Dr. Stockbridge stated it is hard to comment as these questions are all related to review issues. Dr. Stockbridge agrees that the correct development program was undertaken. Both Dr. Hung and Dr. Karkowsky expressed concerns with the efficacy data shown at the low doses with [redacted] but agree that this is a review issue. The sponsor agreed that they are puzzled with the results of the low dose of [redacted] and also with the results of the hydrochlorothiazide monotherapy arm of the trial. However, the sponsor believes that the low dose [redacted] s an acceptable dose as it beats placebo and further illustrated by modeling.

   The sponsor was concerned that if the low dose was not found to be efficacious that it would be detrimental to their proposed bracketing scheme. Dr. Beasley confirmed that using this dose for bracketing would still be acceptable, even if it were not found to be acceptable for approval, as dissolution data are available for approval of the other doses.

5. AstraZeneca proposes to reference NDA 19-962 for metoprolol succinate rather than resubmit the clinical studies for the individual product in the NDA. Does the Agency concur that this is acceptable?

   The Division agrees.

Pharmacology/Toxicology

6. Based on the Agency comments from the 24 January 2003 End of Phase 2 meeting, AstraZeneca proposes to reference NDA 19-962 for metoprolol succinate rather than resubmit the toxicology studies for the individual product in the NDA. Does the Agency concur that cross-referencing the original NDA for Toprol-XL is acceptable?

   The Division agrees.

7. Does the Agency agree that there is sufficient clinical experience with HCT such that a brief overview of the published literature and the summaries of the combination studies conducted with metoprolol (both succinate and tartrate salts) is sufficient for filing the NDA?

   Dr. Stockbridge requested full study reports be submitted. In addition, Dr. Stockbridge inquired if the sponsor had bioavailability and bioequivalence data in animals for the succinate vs. the tartrate salts. The sponsor confirmed that they had this data and will submit it with the NDA.

Request for Waiver of Pediatric Studies

8. AstraZeneca intends to request a waiver of pediatric studies under 21 CFR 314.55(c)(2) and anticipates that the Division will grant such a waiver. Does the Agency have any specific guidance to offer?

   Dr. Stockbridge stated that the granting of a waiver is standard for combination products.

NDA Format

9. AstraZeneca will provide this submission in the Common Technical Document format (CTD). A proposed table of contents for this submission is included in Section 4 of this document. Does the Division find the proposal for presentation of the content acceptable?

   The Division agrees.

10. AstraZeneca intends to follow the folder structure outlined in the January 1999 Guidance for Industry entitled, "Providing Regulatory Submissions in Electronic Format - NDAs." The format of the CTD will follow the August 2001 FDA draft Guidance for Industry entitled "Submitted Marketing Applications According to ICH-CTD Format - General Considerations." Navigation to the module components will be through the module TOCs. Hypertext linking will follow the January 1999 guidance. Does the Agency find the proposal for presenting the submission in electronic format acceptable?

    The Division agrees.

11. Data will be provided as SAS® Version 5 (SAS Institute Inc.) transport files; each filename will include the three letter extension "xpt." Each analysis domain will be provided as a single dataset. All datasets from the study will be placed in a folder identified by the study name. A data definition file will be provided for the study. The data-definition file will describe the purpose of each variable and how each variable has been obtained or derived. Each patient will be identified with a single unique number, trial/center/patient ID. An annotated CRF will also be provided for the study. Does the Division agree with this approach?

    The Division agrees. Dr. Stockbridge requested that all analysis and raw datasets be submitted. In addition, Dr. Stockbridge requested the sponsor submit the SAS code for review.

12. The following information could be available sooner (original NDA Submission Content, see table below) than the drug product and lowest strength bioequivalence study by about three months. Is it possible to submit these modules to the Division earlier and then follow with an amendment approximately 3 months later containing the drug product information and lowest strength bioequivalence study summary, study report, data listings and case report forms?

    Dr. Stockbridge stated he is reluctant to allow the sponsor to submit part of the NDA and then submit critical review parts at a later date. This is sometimes allowed when there is a compelling public health reason and the Agency would not want to hold up drug approval, but that is not the case with this product. However, Dr. Stockbridge encouraged the sponsor to submit available data to the IND for review. Hopefully, this would allow the Division to take an action prior to the 10 month PDUFA clock. Dr. Stockbridge believes it is important for the sponsor to submit a complete NDA package.

13. AstraZeneca proposes to submit updated stability data during the review of the NDA without resulting in a review time delay (data provided 4 months after final submission of Module 3 data). Does the Agency find this proposal acceptable?

    The Division agrees.

Dr. Zimmerman noted some concerns from a CMC perspective. He requested the sponsor include a historical summary with their NDA submission with respect to certain control aspects for which there would be an expected reliance (i.e., drug substance and drug product impurities and degradants) which will allow for ease of review when cross referencing the Toprol XL NDA submission. Dr. Zimmerman also inquired if the sponsor is planning on using different methods for the monotherapy and combination products. The sponsor stated there is a different rotation speed, but they plan to submit a

methods development package which will outline any changes and justify them. Finally, Dr. Zimmerman encouraged the sponsor to look at any potential interaction effects causing new impurities which may be present in the combination product, but were not present in the monotherapies. Dr. Zimmerman suggested this be done under accelerated conditions.

Addendum to Minutes from the Office of Drug Safety:

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:
  RiskMAPs
  2.5.5 Overview of Safety with appropriate cross references to section
  2.7.4 Summary of Clinical Safety
  and any other relevant sections of the Common Technical Document for the NDA/BLA application.
  Pharmacovigilance plans
  2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
  (e.g., module 4 if the study is a nonclinical study).

  If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or
  BLA Clinical Data Section (21 CFR 601.25(b)(3))
  and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at http://www.fda.gov/cder/guidance/5766dft.pdf and http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc .

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 1/24/05 Finaled: 2/1/05

RD:

Stockbridge	1/31/05
Karkowsky	1/31/05
Hung	1/29/05
Zimmerman	1/27/05
Beasley	1/28/05
DeFelice	1/24/05
Joseph	1/24/05

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

/s/

Melissa Robb
2/1/05 08:31:26 AM

Norman Stockbridge
2/2/05 06:56:50 AM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	302-886-2822
Attention:	Ms. Paula Clark
Company Name:	**AstraZeneca**
Phone:	**302-885-1492**
Subject:	**Teleconference Minutes 9/30/04**
Date:	10/4/04
Pages including this sheet:	7
From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Teleconference

Meeting Date:	September 30, 2004
Drug:	Toprol XL (metoprolol succinate) ER Tablets & hydrochlorothiazide (HCT) Tablets
Sponsor:	AstraZeneca

FDA Participants:

Patrick Marroum, Ph.D.	Team Leader, Biopharmacuetics, HFD-860
Nhi Beasley, Pharm.D.	Pharmacokineticist, HFD-860
Donald Schuirmann	Mathematical Statistician, HFD-705
Melissa Robb	RHPM, HFD-110

AstraZeneca Participants:

Ms. Cindy Lancaster	Director, Regulatory Affairs
Ms. Paula Clark	Associate Director, Regulatory Affairs
Ms. Jennifer Sugg	Senior Statistical Scientist
Dr. Maria Sunzel	Director of Pharmacology and Experimental Medicine
Ms. Solveig Billing Claesson	Experimental Medicine Leader
Dr. James Hainer	Director, Clinical Research

Background:
In a submission dated July 19, 2004, the sponsor included a new protocol entitled, "A Single Dose Bioequivalence Study Comparing Two Fixed Combination Tablets of Extended Release Metoprolol Succinate/Hydrochlorothiazide (HCT) 23.75 mg/6.25 mg to the Free Combination of Metoprolol Succinate (Seloken ZOC/Toprol-XL 2 x 23.75 mg) plus HCT (2 x 6.25 mg)". This teleconference was requested by the Division in order to discuss some concerns with this protocol.

Meeting:
The sponsor began by acknowledging there was a mistake in Table 1 of the calculations for rejecting the null hypothesis included in their response emailed to the Agency dated September 28, 2004 (Attachment 1). The sponsor would like to use the level of significance that was provided in the comments from the Agency for the sponsor to review (Attachment 2).

Mr. Schuirmann stated that in his comments he attempted to determine what level of significance would correspond to their proposed critical values using the z-test, while using the t-test. The values he provided were only starting values to be used to determine correct values. The sponsor stated they had run simulations and believe the overall error rate is 0.0498. Therefore, they would like to use the three probability values proposed by Mr. Schuirmann; 0.00921 for Stage 1, rejecting the null, 0.58473 for Stage 1, stopping the study, and 0.04776 Stage 2, rejecting the null. Mr. Schuirmann stated he would like to verify these numbers are acceptable. The sponsor clarified that instead of using the value noted for stopping the study at the first stage, 0.58473, they plan to use the converse or 1-0.58473.

Mr. Schuirmann then discussed Table 1, which was included in the sponsor's response. The sponsor has both an "A" hypothesis and a "B" hypothesis outlined. In the "A" hypothesis, the test would be stopped at Stage 1 and equivalence would be concluded if <-2.357 occurred, resulting in a probability of 0.01884. In addition, the test would be stopped at Stage 1 and equivalence would not be concluded if >0.214 occurred, with an upper level of significance of 0.41585. For hypothesis "B", the same is true with an inverse of the signs. After further discussion, it was noted that all were in agreement and that the sponsor would not stop for futility unless the estimate was worse than the 0-the log 1.25.

Mr. Schuirmann stated that in the original protocol submitted dated July 19, 2004, the rules for interim analysis were very clearly stated.

The next issue discussed was that of the conduct of the study. It was noted the sponsor plans to recruit 44 patients for Stage 1. Mr. Schuirmann stated that if the sponsor uses different periods for evaluation, this will result in a change in the degrees of freedom. Mr. Schuirmann stated that if the sponsor performs the trial in groups which start on different calendar days, they will need to account for this in their statistical model. Dr. Marroum deferred to Mr. Schuirmann as this is a statistical issue, but stated that they have seen only 1-2 bioequivalence protocols that were this large and that encountered this issue. In those cases, they also had to adjust for studying the groups on different days. Mr. Schuirmann clarified that it would be acceptable to perform the test recruiting all the patients at one time and then assigning them randomly to groups. However, the model would need to account for the groups starting on different calendar days. Mr. Schuirmann added that the sponsor should use restricted randomization to ensure that each subject would have an equal chance in being in any bin.

The sponsor inquired if it would be acceptable to recruit and randomize all the participants for Stage 1 and then recruit and randomize all the patients for Stage 2, if needed. Dr. Marroum stated this would be acceptable, providing that they recruit from a similar pool.

The sponsor agreed to amend the protocol to add the term "period within group" to the model. The sponsor agreed this would change the degrees of freedom and the critical values. Mr. Schuirmann stated he did not believe it would be necessary to add a stage term to the model. He believed that since the different stages are also different groups the term "period within group" would be sufficient. However, Mr. Schuirmann stated the sponsor could add a term for the differing stages if they preferred. Mr. Schuirmann added that in the past he has seen a period effect in bioequivalence studies.

The sponsor will submit to the Agency a proposal of alpha levels, for all three tests, to be reviewed by Mr. Schuirmann after performing simulations.

The sponsor inquired about declaring bioequivalence for this drug product. The sponsor was concerned since metoprolol is extended release that the Cmax may not be bioequivalent during Stage 1, and wanted to know if the Agency suggested automatically going to Stage 2. Dr. Marroum stated that if the tablets are not bioequivalent in terms of Cmax, then the formulation would be declared bioinequivalent. The clinical division would then have to decide if the difference in Cmax is acceptable. The sponsor inquired if after determining their Stage 1 results, they could discuss them with the Agency if they missed on Cmax. Dr. Marroum agreed.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 9/30/04 Finaled: 10/1/04

RD:

Schuirmann	9/30/04
Marroum	10/1/04
Nguyen	10/1/04

Attachment 1

IND 67,095

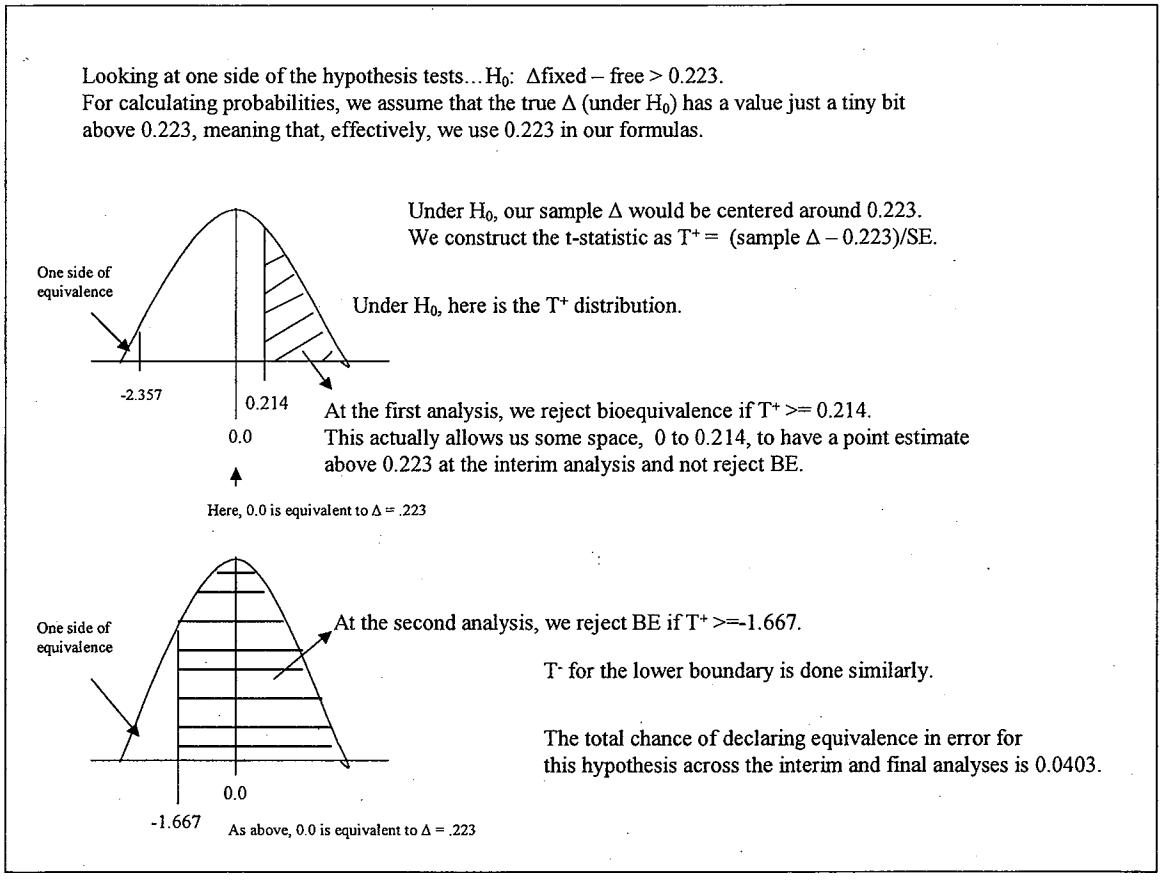
Toprol-XL® (metoprolol succinate) ER and hydrochlorothiazide in combination Tablets

Response to Statistical Comments for Teleconference on September 30, 2004

In response to the questions and issues raised, we would like to share additional information for the critical values for decision-making and the probabilities for overall error in rejecting the null hypotheses for inequivalence. Following the statistical information, an explanation is offered regarding the questions concerning recruitment. We submit this information so that it might provide background on the rationale for the planned statistical analysis and that it might aid the discussion during this Thursday's teleconference.

First, we would like to respond to the second sentence of the second paragraph. We did intend to use a cut-off of 0.214 during the interim analysis to conclude inequivalence. The figure below is one that we have used internally to describe the statistical analysis. We include it here to help illustrate our plans.

Figure 1 Illustration of the Decision Rules for the Interim and Final Analyses



Secondly, we agree that it might be more appropriate to set nominal levels of significance for each set of one-sided tests, rather than using critical values. However, we do believe that if the planned numbers of subjects were achieved, that the overall error rate would be <0.05. We did not conduct any simulations, but would like to share our probability calculations here so that differences might be identified.
Probability calculations are conducted under the upper one-sided null hypothesis, assuming that the true difference between the fixed combination and free combination is 0.223.

Table 1 Calculation of Probabilities for Error in Rejecting Null Hypothesis (Inequivalence) when True Difference Between Formulations is 0.223.

Prob(rejecting null during the interim analysis)	$= \text{Prob}(T_{38} \leq -2.357)$
	$= 0.01184$
Prob(continuing beyond interim analysis)	$= 1 - [\text{Prob}(\text{reject null during interim}) + \text{Prob}(\text{accepting null during interim})]$
	$= 1 - \text{Prob}(T_{38} \leq -2.357) - \text{Prob}(T_{38} \geq 0.214)$
	$= 1 - 0.01184 - 0.41585$
	$= 0.57231$
Prob(rejecting null during second analysis)	$= \text{Prob}(\text{continuing beyond interim analysis}) * \text{Prob}(T_{78} \leq -1.667)$
	$= 0.57231 * 0.04976$
	$= 0.02848$
Total probability of rejecting null hypothesis when true difference is 0.223	$= \text{Prob}(\text{rejecting null during interim analysis}) + \text{Prob}(\text{rejecting null during second analysis})$
	$= 0.01184 + 0.02848$
	$= 0.04032$

We offer the following explanation in regard to the question from Dr. Schuirmann's 'Additional questions concerning recruitment'. As is usual for bioequivalence studies being conducted in healthy volunteers, the investigational site attempts to identify and screen the entire requisite study sample size and to complete the study within a short time period. A similar approach will be followed in the planned study with a projected time to complete the study in Group 1 (n = 44) of 4 weeks. (If a second group is needed, it will also be conducted within a similar short time period.) As is also typical for these studies, practical logistical and scheduling considerations dictate that the investigator divide the study population into several cohorts of a convenient size with each scheduled to start on specified calendar days. The study does not, however, employ a 'rolling recruitment' strategy in which subjects are enrolled 'one-at-a-time' as they are found. Importantly, all subjects undergo the same procedures at the same site conducted by the same personnel.

Attachment 2

The sponsor is to be commended for proposing a group sequential approach, making adjustments to the nominal level of significance to be used after each stage of the proposed two-stage BE study in order to ensure that the overall level of significance is controlled at 0.05.

The numbers presented in the sponsor's proposal do not appear to actually achieve this objective. The sponsor's proposed critical values - 2.357 for concluding equivalence at stage one, 0.214 (actually -0.214) for concluding inequivalence at stage one, and 1.667 for concluding equivalence at stage two - do not appear to achieve an overall level of significance of 0.05. The actual level, based on simulations and numerical calculations I have carried out, appears to be in the neighborhood of 0.055 (based on an assumption of 40 subjects in each stage, and an assumed intra-subject CV of 27%.)

These calculations assume that the two one-sided tests will be t-tests. But if we had a case of known variance (we don't), then the two one-sided tests would be z-tests, and then the sponsor's proposed critical values would be approximately correct for achieving an overall level of 0.05 (though not ***exactly*** correct.)

So a good place for the sponsor to start would be to replace their proposed critical values with corresponding values appropriate to the t-distribution. The upper-tail probability associated with the sponsor's proposed critical values are

critical value	normal distribution upper-tail probability
2.357	0.00921
-0.214	0.58473
1.667	0.04776

If 40 subjects are studied in stage one of the proposed study, there are possibly 38 degrees of freedom for residual error. The critical value of the t-distribution with 38 degrees of freedom corresponding to p=0.00921 is approximately 2.46305, and the critical value corresponding to 0.58473 is approximately -0.21549. If there are also 40 subjects in stage two, then there are possibly 77 degrees of freedom for the stage two t-tests (these degrees of freedom at each stage actually depend on the exact conduct of the study), and the critical value corresponding to p=0.04776 is approximately 1.68768. So replacing the proposed critical values of 2.357, -0.214, and 1.667 with 2.46305, -0.21549, and 1.68768 would be a first step toward achieving an overall level of significance of 0.05.

However, we would like the sponsor to fine-tune the proposed critical values (or, perhaps more appropriately, the proposed nominal levels of significance for each set of one-sided tests), in order to achieve the desired overall level of no more than 0.05 more precisely. We would also like to see some indication of the sensitivity of the chosen critical values/individual levels of significance to the possible sample sizes that may be achieved in the proposed study - for example, suppose they end up with
39 subjects in stage one and 43 subjects in stage two. Would the proposed test levels still work?

Additional questions concerning recruitment

Are they planning (in each stage) to recruit 44 subjects and begin studying them all on the same calendar day? Are they planning to break up this group of 44 into two or more groups (for example, 22 in a first group and 22 in a second group)? Or are they planning to use "rolling recruitment", in which subjects are studied "as they are found", with most subjects starting the study on different calendar days? Answers to these questions have implications for the details of the statistical analysis.

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/s/

Melissa Robb
10/4/04 10:11:37 AM

Patrick Marroum
10/13/04 05:42:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising and Communication

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Alisea Sermon
ODE I/Division of Cardio-Renal Products
(301) 796-1144

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12.15.05	67,095	21-956	Labeling Review for NDA	10.28.05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Metoprolol succinate/HCTZ ER	S	4, Combination Product	6.1.2006

NAME OF FIRM: AstraZeneca LP

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Labeling consult; Please access the EDR for all labeling submissions

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Alisea Sermon, PharmD	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Alisea Sermon
12/19/2005 11:09:58 AM

ATTACHMENT

MEMO OF FILING MEETING

DATE: **December 2, 2005**

BACKGROUND: **AstraZeneca LP submitted a NDA for Metoprolol Succinate ER/Hctz 25/12.5 mg and 100/12.5 mg pursuant to section 505b(1) of the Federal Food and Drug Administration Act. Reference is made to IND 67,095 to investigate the oral administration to adults of the combination of metoprolol succinate ER and hydrochlorothiazide for the management of hypertension.**

ATTENDEES:	Norman Stockbridge, M.D., Ph.D.	Acting Division Director
	Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
	Akinwole Williams, M.D.	Medical Officer
	Patrick Marroum, Ph.D.	Clinical Pharmacologist
	Xavier Joseph, Ph.D.	Pharmacologist
	John Lawrence, Ph.D.	Statistician
	Ququan (Cherry) Liu, Ph.D.	Statistician
	Haripada Sarker, Ph.D.	Chemist

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	Reviewer	Projected Goal Date
Medical:	**Akinwole Williams, M.D.**	**May 30, 2006**
Secondary Medical:	**N/A**	
Statistical:	**Cherry Liu, Ph.D.**	**April 30, 2006**
Pharmacology:	**Xavier Joseph, Ph.D.**	**June 30, 2006**
Statistical Pharmacology:	**N/A**	
Chemistry:	**Haripada Sarker, Ph.D.**	**June 28, 2006**
Environmental Assessment (if needed):	**N/A**	
Biopharmaceutical:	**Lydia Velazquez, PharmD**	**June 30, 2006**
Microbiology, sterility:	**N/A**	
Microbiology, clinical (for antimicrobial products only):	**N/A**	
DSI:	**Sharon Gershon, Pharm.D.**	**June 30, 2006**
Regulatory Project Management:	**Alisea Sermon, Pharm.D.**	**June 30, 2006**
Other Consults:	**N/A**	

Per reviewers, are all parts in English or English translation? YES	☒	NO	☐

If no, explain:

CLINICAL FILE	☒	REFUSE TO FILE	☐

• Clinical site inspection needed? YES	☒	NO	☐

• Advisory Committee Meeting needed? YES, date if known			NO	☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A	☒	YES	☐	NO	☐

CLINICAL MICROBIOLOGY **N/A**	☒	FILE	☐	REFUSE TO FILE	☐
STATISTICS N/A	☐	FILE	☒	REFUSE TO FILE	☐
BIOPHARMACEUTICS FILE	☒			REFUSE TO FILE	☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A	☒	FILE	☐	REFUSE TO FILE	☐

• GLP inspection needed? YES	☐	NO	☐

CHEMISTRY	FILE	X☐	REFUSE TO FILE	☐

• Establishment(s) ready for inspection? YES	☐	NO	☐

- Microbiology **N/A** YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: No

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
☐	No filing issues have been identified.

☐	Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues to applicant by Day 74.

Alisea Sermon, Pharm.D.
Regulatory Project Manager, HFD-110

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/s/

Alisea Sermon
12/16/2005 03:18:19 PM