CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-956

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 21-956/N000	SUBMISSION DATE	October 28, 2005
N000C		April 17, 2006
N000BM		April 19, 2006
N000C		May 1, 2006
N000BB		May 1, 2006
N000BC		May 15, 2006
N000C		May 19, 2006
N000C		May 19, 2006
N000BB		June 12, 2006
N000BL		June 26, 2006
N000C		August 3, 2006
N000BB		August 8, 2006

TYPE: ORIGINAL NEW DRUG APPLICATION

BRAND NAME: Dutoprol® Tablets
GENERIC NAME: Metoprolol Succinate extended-release/Hydrochlorothiazide immediate release

DOSAGE STRENGTH: 25/12.5, 50/12.5, 100/12.5 mg, respectively
INDICATION: Management of hypertension in adults, the fixed-dose combination is not indicated for initial therapy.

SPONSOR: AstraZeneca, LP

PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.
TEAM LEADER: Patrick Marroum, Ph.D.

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Executive Summary

AstraZeneca is seeking approval of Dutoprol (metoprolol succinate extended release (CR)/hydrochlorothiazide (HCT) immediate-release (IR)) tablets. This new formulation combines a $beta_1$-selective adrenoceptor blocking agent and a thiazide diuretic, HCT. The sponsor is seeking an indication for the treatment of hypertension. The submitted NDA application is for a combination product to be taken orally. Dutoprol has been developed in four tablet strengths for oral administration of metoprolol succinate CR and HCT: the 25/6.25 mg strength contains 23.75 mg of metoprolol succinate CR equivalent to 25 mg of metoprolol tartrate and 6.25 mg of HCT; the 25/12.5 mg strength contains 23.75 mg of metoprolol succinate CR equivalent to 25 mg of metoprolol tartrate and 12.5 mg of HCT; the 50/12.5 mg strength contains 47.5 mg of metoprolol succinate CR equivalent to 50 mg of metoprolol tartrate and 12.5 mg of HCT, the 100/12.5 mg strength contains 95 mg of metoprolol succinate extended release equivalent to 100 mg of metoprolol tartrate and 12.5 mg of HCT. The lowest 25/6.25 mg strength will not be marketed in the U.S.; but was used by the sponsor to perform a bioequivalence study with the lowest and highest (95/12.5 mg) strength in order to request a biowaiver of additional clinical studies for the two intermediate strengths (23.75/12.5 mg and 47.5/12.5 mg) since the four strengths are not compositionally proportional. In total, the sponsor has submitted 8 clinical studies to the NDA; which includes a phase III study (Study 324–ATTACH) with no pharmacokinetic content. Study 324 included a factorial design that investigated the antihypertensive efficacy of the combination in comparison to that of the individual agents. This factorial design study was conducted with the individual component agents used in combination.

Section 6 of NDA 21-956 includes 7 studies, along with dissolution data and biowaiver analyses of the intermediate strengths. Three of the studies (S895, S-896, and S897) submitted utilized an earlier formulation of the fixed combination product metoprolol succinate CR/HCT. As a result a fourth study (study S-998) was conducted to demonstrate bioequivalence between the product in earlier studies and the formulation of the fixed combination product that was used in study S902 that is the "to-be-marketed" formulation. Studies D4026C00005 and D4026C00006 were conducted later in order to demonstrate bioequivalence between the clinical trial (Study 324-ATTACH) formulation and the "to-be-marketed" formulation.

A literature search was performed by the reviewer for completeness sake in order to update the proposed package labeling; but no reports were found from the clinical pharmacology perspective.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-956 submitted on October 28, 2005, April 17, 19, May 1 (N000 C and BB), May 15, 19 (N000 C and C), June 12, 26, August 3 (N000C), and an e-mail dated August 8, 2006 for Dutoprol® tablets and has the following clinical pharmacology and biopharmaceutics comments:

REVIEWER COMMENTS TO THE SPONSOR:

The following Comments should be addressed by the sponsor:

1. Biowaiver:

A biowaiver to perform additional bioequivalence studies of the intermediate strengths (Metoprolol CR/HCT - 23.75/ 12.5 mg and 43.75/12.5 mg, respectively) is granted.

2. Dissolution

The sponsor's proposed dissolution methods and specifications for the **MET CR** component of Dutoprol is as follows:

Apparatus	*USP Apparatus II (paddle)*
Speed	*75 rpm*
Medium	*Sodium Phosphate Buffer Solution, pH 6.8*
Volume	*500 mL*
Temperature	*37° C ± 0.5° C*

Q	*1 hour*	*NMT*	*of label claim*
	4 hours		*of label claim*
	8 hours		*of label claim*
	20 hours	*NLT*	*of label claim*

USP recommendations for metoprolol succinate ER dissolution methods and specifications are as follows:

Apparatus	*USP Apparatus II (paddle)*
Speed	*50 rpm*
Medium	*Potassium Phosphate Buffer Solution, pH 6.8*
Volume	*500 mL*
Temperature	*37° C ± 0.5° C*

Q	*1 hour*	*NMT 25% of label claim*
	4 hours	*20 to 40% of label claim*
	8 hours	*40 to 60% of label claim*
	20 hours	*NLT 80% of label claim*

After reviewing all metoprolol succinate dissolution raw data:

- The proposed 20 hour time specification can be tightened-up to 18 hours since the dissolution profile seems to reach an asymptote by that time point and in order to allow for more discriminatory assessment for quality control purposes.

As a result, the dissolution method and specifications for the metoprolol succinate ER component of Dutoprol is as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	75 rpm	
Medium	Sodium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT of label claim
	After 4 hours	of label claim
	After 8 hours	of label claim
	After 18 hours	NLT of label claim

The sponsor's proposed dissolution methods and specifications for the **HCT** component of Dutoprol is as follows:

Apparatus	USP Apparatus [redacted]
Speed	100 rpm
Medium	0.1 M HCl
Volume	[redacted]
Temperature	37° C ± 0.5° C
Q	NLT [redacted] minutes

USP recommendations for HCT dissolution methods and specifications are as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT 80% in 60 minutes

In reviewing the submitted data by e-mail dated August 8, 2006:

1) The new specifications of a Q of NLT [redacted] ninutes is not appropriate since it is evident from the raw data submitted that all units tested dissolved at a rate of [redacted] or more within [redacted] minutes and is the basis for the sponsor not performing an F_2 similarity factor calculation for HCT for biowaiver purposes (see F_2 similarity Factor and Biowaiver section).
2) In addition, the sponsor's submitted data justifying no need for the F_2 similarity Factor utilized dissolution media in a volume of 900 mL.

As a result, the dissolution method and specifications for the HCT component of Dutoprol is as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT [redacted] minutes

3. <u>Tablet Composition</u>

The sponsor should submit total weight for all tablet strengths of Dutoprol formulation.

4. <u>Labeling:</u>

1. The following statement should be changed in the "PHARMACOKINETIC" section of the proposed label in order to align itself with findings in study D4026C00005:

Proposed by Sponsor:
Pharmacokinetics

Recommended by Agency:
Pharmacokinetics

The rate and extent of absorption of metoprolol/ hydrochlorothiazide are similar in the fasting state and after a high-fat meal when given as TRADE NAME tablets. (See DOSAGE AND ADMINISTRATION.)

Single dose pharmacokinetics of metoprolol/hydrochlorothiazide given as TRADE NAME tablets is similar to that of each drug given individually as Toprol XL® and a formulation of hydrochlorothiazide created for the clinical trial ATTACH.

2. The following statement should be changed in the "PHARMACOKINETIC" section of the proposed label for better clarity:

Proposed by Sponsor:
Pharmacokinetics

Recommended by Agency:
Pharmacokinetics
Metoprolol succinate extended release

3. The following comment should be added to the "WARNING" section of the proposed label in order to direct the reader to the appropriate section corresponding to the dosage adjustment statement:

Proposed by Sponsor:
Hydrochlorothiazide

Recommended by Agency:
Hydrochlorothiazide
Renal Disease: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function *(see DOSAGE AND ADMINISTRATION).*

Hepatic Disease: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma *(see DOSAGE AND ADMINISTRATION).*

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____

OCPB Briefing was held on July 25, 2006. Attendees were: L. Velazquez, M. Mehta, P. Marroum, N. Stockbridge, J. Katahara, G. Williams, A. Williams, and J. Lawrence.

CC list: HFD-110: NDA 21-956 (SermonA, StockbridgeN); HFD-860: (VelazquezL, MarroumP, MehtaM); CDER Central Document Room

Summary of Important CPB Findings

Exposure-response relationship: A dose-related blood pressure lowering effect was observed across the two clinical studies (studies 324 and S-902). Study 324 was a dose ranging study in the targeted population using a factorial design to explore dosing. ANCOVA analysis demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. The four treatment combinations of Toprol XL/HCT 100/6.25mg, 100/12.5mg, 100/25mg, and 200/25mg had significantly greater reductions than both of their respective components at significance level of <0.05.

In study S-902, two combinations of metoprolol were studied (metoprolol succinate ER/HCT 100/12.5mg and conventional metoprolol tartrate IR/HCT 100/12.5mg. This study also had a run-in period where HCT 12.5mg once daily was administered. The MET CR/HCT dose selected for this trial was the only combination dose level available at the time of the study and was approved only outside the U.S.

Exposure-response support of dosing regimen: Once daily dosing is supported by study 324 clinical trial findings (peak:trough BP ratio close to 1.0 between baseline and week 8). The clinical trial findings supporting once daily dosing are also consistent with the 24 hour pharmacokinetic and pharmacodynamic profiles of the individual agents and the combination found in other pharmacokinetic studies.

Once daily dosing is partially supported by pharmacokinetic findings in study D4026C000006 where mean metoprolol plasma concentration-time-curves for the fixed and free combination tablet strength of MET CR/HCT tablet 23.75/6.25mg (administered as two tablets from study D4026C00006) are sustained over a 24-hour dosing interval.

In study S-902 the effect on BP and HR 24 hours post dose of the new combination versus the conventional combination (metoprolol tartrate/HCT – both IR formulations) of metoprolol 100 mg and HCT 12.5 mg in patients with essential hypertension resulted in similar beta-blockade. However, the assessment of sufficient BP and HR controlled at the end of the 24-hour dosing period was not formally addressed.

Consistency of a CR formulation for the MET CR component of the drug product: In Study S-902, the plasma concentration of metoprolol, 24 hours after administration of the new combination product of metoprolol CR 100 mg and HCT 12.5 mg with that of the conventional combination of metoprolol conventional tablets 100 mg and HCT 12.5 mg in patients with essential hypertension was investigated resulting in higher sustained mean trough concentrations of metoprolol with the new fixed formulation when compared to the conventional formulation (95.9 versus 40.6 nmol/L). However, the sponsor measured metoprolol concentrations strictly as a compliance method.

In study D4026C00005 and D4026C00006 bioequivalence was established between Toprol XL and the metoprolol succinate extended-release component of Dutoprol.

Evidence of a Drug Interaction between Metoprolol and HCT: A drug interaction was performed between metoprolol and HCT resulting in insignificant differences in the pharmacokinetic changes observed:

Study code No. of centers Locations Study timeline	Primary objective	Study design Duration	No. of patients Age, years (range)	Treatments	Results
S-895 One (1) center Mölndal, Sweden Study start: 27 Feb 1987 Study end: 16 July 1987	To determine (1) the relative oral bioavailability of metoprolol given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg and as metoprolol CR 100 mg alone; and (2) the relative oral bioavailability of HCT given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg, as a HCT 12.5 mg tablet and as Esidrex® 25 mg tablet.	A 4-way, randomized, open, crossover bioavailability study Once-daily doses for 5 days; 24-h PK sampling at steady state (Day 5).	12 healthy men Mean age 27 (24 to 34)	Each subject received 4 treatments (>5-day washout in-between): Metoprolol ER 100 mg alone; HCT 12.5 mg (IR) alone, HCT 25 mg [Esidrex®] alone; Test: Fixed combination tablet of metoprolol-ER/HCT 100/12.5 mg	The AUC of metoprolol/HCT were similar given in combination (test) vs. as single agents (reference). C_{max} was somewhat lower for both HCT and metoprolol when given as a combination tablet. Conclusion: metoprolol/HCT in combination were bioequivalent with regard to AUC to each mono component. There was no significant pharmacokinetic interaction between HCT and metoprolol when given as the combination.

The decrease in metoprolol C_{max} was 23% when metoprolol succinate was administered with HCT (249 versus 191 nmol/L alone versus with HCT). T_{max}, C_{min} and AUC remained unchanged. HCT C_{max} decrease was about 16% when coadministered (331 versus 279 nmol/L) with metoprolol. T_{max}, C_{min} and AUC remained unchanged. Both changes are of no clinical significance.

Demonstration of Bioequivalence: Since the different strengths of the "to-be-marketed" formulations are not compositionally proportional, two bioequivalence studies (D4026C00005 and D4026C00006) were performed involving the highest and lowest strength (MET CR/HCT 100/12.5mg and 25/6.25mg, respectively) with an intent by the sponsor to request a biowaiver for the two intermediate strengths (25/12.5mg and 50/12.5mg, respectively).

In study D4026C00005 bioequivalence was demonstrated with the highest dose by way of a single-dose, randomized, open-label, 4-way cross-over, fed and fasted study in 48 healthy volunteers. Metoprolol C_{max} 90% CI was 103 to 118, while the CI for AUC_{0-t} was 94 to 105% and for $AUC_{0-\infty}$ 94 to 105% as well. HCT also demonstrated bioequivalent with regard to C_{max} (90% CI 101 to 114%), AUC_{0-t} (100 to 108% CI), and $AUC_{0-\infty}$ (100 to 108%) in the fasted state.

In study D4026C00006, bioequivalence was evaluated with the lowest MET CR/HCT combination (fixed or free combination) of 25/6.25mg (given as 2 X 25 mg/6.25 mg). This was a single-dose, randomized, open-label, 2-way cross-over, fasted study in 44 healthy volunteers. Metoprolol C_{max} 90% CI was 84 to 97%, while the CI for AUC_{0-t} was 94 to 105% and for $AUC_{0-\infty}$ 94 to 105% as well. HCT also demonstrated bioequivalent with regard to C_{max} (90% CI 88 to 99%), AUC_{0-t} (93 to 103% CI), and $AUC_{0-\infty}$ (93 to 103%).

Food effect: Food had little impact on the rate and extent of absorption of Dutoprol (D4026C00005). Metoprolol C_{max} fasted versus fed was 121 and 118 nmol/L, respectively with a CV% of 87 and 75.1%. Tmax was 10.38 versus 8.15 hours (fasted to

fed) with a CV% of 35.7 and 54.3%. AUC_{0-t} was 2440 versus 2362 nmol·h/L with a CV% 97.5 and 91.7%. $AUC_{0-\infty}$ was 2583 versus 2505 nmol·h/L with a CV% of 97.8 and 92.4%. All pharmacokinetic variables had a high CV%. HCT C_{max} differences were about 14% (268 versus 231 nmol/L, fasted to fed), AUC_{0-t} was 1941 versus 1809 nmol·h/L, and $AUC_{0-\infty}$ was 2046 versus 1920 nmol·h/L. The CV% was not high and remained consistent throughout all pharmacokinetic parameters. The high CV% observed with metoprolol pharmacokinetic parameters may have been due to CYP2D6 polymorphism making clinical impact of the variability negligible.

Dose dumping: The new formulation was compared to Toprol XL in fed and fasted conditions in the above mentioned study (D4026C00005) resulting in no pharmacokinetic differences between the two products or evidence of dose dumping.

Biowaivers for Intermediate strengths: F_2 similarity data was submitted for the Metoprolol component demonstrating similarity between the lowest reference (23.75/6.25mg) and next to lowest strength (23.75/12.5 mg) combination formulation. Similarity was also demonstrated between the highest strength reference (95/12.5 mg) and the next to highest strength (47.5/12.5 mg) combination formulation through a F_2 similarity comparison as well. No F_2 similarity comparison was necessary for the HCT component of the formulation since HCT dissolved by NLT [redacted] minutes in all media tested. As a result, a waiver of biostudies for the intermediate strengths (23.75/12.5 mg and 47.5/12.5 mg) is granted.

Relative Bioavailability: Both components of Dutoprol demonstrated bioequivalence in relation to the clinical trial formulation (D4026C00005 and C00006) indicating that it would be expected that the rate and extent of absorption of both components of Dutoprol would be the same as their individual counterparts. Point estimates for the fixed in relation to the free combination for metoprolol was 0.99 under fasted conditions and 0.98 under fed conditions. Point estimates for HCT were 1.04 for fasted versus 0.99 under fed conditions. Both studies were single dose studies.

Compositional Content of Formulation: The formulation "compositional content" information for all four strengths lacked total weigh for each individual strength so assessment of tablet total weight and size is not possible.

Assay Validation: In studies D4026C00005 and D4026C00006 metoprolol plasma concentrations were assessed by a LC-MS/MS method that was validated in the range of 0.5 to 600 nmol/L and HCT plasma concentrations were assessed by a [redacted] method and validated in the range of 0.5 to 600 nmol/L. In study S-896, there were inconsistencies reported in the assay validation study results for both metoprolol and HCT leading to confusion on what the sponsor reported. As a result, a clear assessment of assay validation is not possible. Study S-897 had missing HCT in urine assay methodology data because the sponsor is unable to locate any study specific validation reports. As a result, the sponsor is proposing that the review of this study for HCT be based on the plasma data and no urine data. A true assessment of assay methodology and validation in studies S896, S-897, and S-998 is not possible. Studies D4026C00005 and D4026C00006 had inconsistencies in how they reported the recovery of HCT in plasma because it was reported for a finite range and not the full

linearity range they claim to have achieved with their assay. As a result, validation of HCT in plasma assay methodology is not possible.

Dissolution: The dissolution methods and specifications proposed by the sponsor are different for the metoprolol succinate ER component and the HCT component.

The sponsor's proposed dissolution methods and specifications for the **MET CR** component of Dutoprol is as follows:

Apparatus	*USP Apparatus II (paddle)*
Speed	*75 rpm*
Medium	*Sodium Phosphate Buffer Solution, pH 6.8*
Volume	*500 mL*
Temperature	*37° C ± 0.5° C*

Q	*1 hour*	*NMT — of label claim*
	4 hours	*— of label claim*
	8 hours	*of label claim*
	20 hours	*NLT — % of label claim*

USP recommendations for **metoprolol** succinate ER dissolution methods and specifications are as follows:

Apparatus	*USP Apparatus II (paddle)*
Speed	*50 rpm*
Medium	*Potassium Phosphate Buffer Solution, pH 6.8*
Volume	*500 mL*
Temperature	*37° C ± 0.5° C*

Q	*1 hour*	*NMT 25% of label claim*
	4 hours	*20 to 40% of label claim*
	8 hours	*40 to 60% of label claim*
	20 hours	*NLT 80% of label claim*

After reviewing all metoprolol succinate dissolution raw data:

- The proposed 20 hour time specification can be tightened-up to 18 hours since the dissolution profile seems to reach an asymptote by that time point and in order to allow for more discriminatory assessment for quality control purposes.

As a result, the dissolution method and specifications for the **metoprolol** succinate ER component of Dutoprol is as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	75 rpm	
Medium	Sodium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT — of label claim
	After 4 hours	— % of label claim
	After 8 hours	% of label claim
	After 18 hours	NLT — of label claim

The sponsor's proposed dissolution methods and specifications for the **HCT** component of Dutoprol is as follows:

Apparatus	USP Apparatus [redacted]
Speed	100 rpm
Medium	0.1 M HCl
Volume	[redacted]
Temperature	37° C ± 0.5° C
Q	NLT [redacted] minutes

USP recommendations for **HCT** dissolution methods and specifications are as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT 80% in 60 minutes

In reviewing the submitted data for HCT and checking the "Guidance for Industry – Dissolution Testing of Immediate Release Solid Oral Dosage Forms":

1) According to the above mentioned guidance, "dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-minute intervals, to generate a dissolution profile". The sponsor's recommendation for Apparatus [redacted] at a speed of 100 rpm is not a speed that is recommended by the guidance as being "mild test conditions" and is not a method that would be considered discriminatory enough. In addition, USP recommendation of Apparatus I at a speed of 100 rpm is part of the quality control dissolution test described in the USP and seems to provide adequate dissolution results according to the data submitted by the sponsor.
2) The new specifications of a Q of NLT [redacted] minutes is not appropriate since it is evident from the raw data submitted that all units tested dissolved at a rate of [redacted] or more within [redacted] minutes and is the basis for the sponsor not performing an F_2 similarity factor calculation for HCT for biowaiver purposes (see F_2 similarity Factor and Biowaiver section).
3) The dissolution volume utilized in the biowaiver study results data was 900mL, not [redacted] In order to align the dissolution methods and specifications with the data utilized for obtaining a biowaiver, the volume to be utilized for dissolution method will be 900 mL.

As a result, the dissolution method and specifications for the **HCT** component of Dutoprol is as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT [redacted] minutes

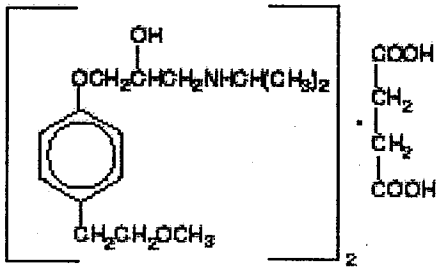
QUESTION BASED REVIEW

I. GENERAL ATTRIBUTES OF THE DRUG

A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG SUBSTANCE?

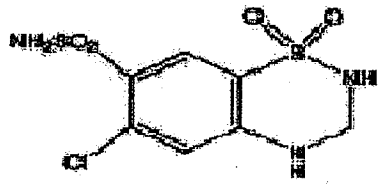
[redacted] (metoprolol succinate extended release (CR)/hydrochlorothiazide) combines a $beta_1$-selective adrenoceptor blocking agent and a diuretic, hydrochlorothiazide.

Metoprolol succinate is chemically described as (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

A. WHAT ARE THE HIGHLIGHTS OF THE FORMULATION OF THE DRUG PRODUCT?

The sponsor has developed a combination product with an extended-release component of metoprolol succinate and immediate-release component of hydrochlorothiazide film-coated tablets. Dutoprol was developed in four tablet strengths for oral administration of metoprolol succinate CR and hydrochlorothiazide: the 25/6.25 mg strength contains 23.75 mg of metoprolol succinate CR equivalent to 25 mg of metoprolol tartrate and 6.25 mg of hydrochlorothiazide; the 25/12.5 mg strength contains 23.75 mg of metoprolol succinate CR equivalent to 25 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide; the 50/12.5 mg strength contains 47.5 mg of metoprolol succinate CR equivalent to 50 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide, the 100/12.5 mg strength contains 95 mg of metoprolol succinate extended release equivalent to 100 mg of metoprolol tartrate and 12.5 mg of hydrochlorothiazide. The lowest 25/6.25 mg strength will not be marketed in the U.S. but is included in this document since it was used in some of the studies reviewed.

The four strengths are not compositionally proportional as demonstrated below. The inactive ingredients of the tablets are silicon dioxide, ethylcellulose, hydroxypropyl cellulose, cornstarch, microcrystalline cellulose, polyvinyl pyrrolidone, sodium stearyl fumarate, hydroxypropyl methylcellulose, polyethylene glycol 6000, titanium dioxide, iron oxide (yellow), iron oxide (red) and paraffin.

	Strength (mg)					
	23.75/6.25	23.75/12.5	47.5/12.5	95/12.5		
Components	Quantity (mg/tablet)	Quantity (mg/tablet)	Quantity (mg/tablet)	Quantity (mg/tablet)	Function	Standard

	Strength (mg)					
Components	23.75/6.25 Quantity (mg/tablet)	23.75/12.5 Quantity (mg/tablet)	47.5/12.5 Quantity (mg/tablet)	95/12.5 Quantity (mg/tablet)	Function	Standard

Total weight of each strength of tablet was not provided by the sponsor.

Tablet Strength (mg)	23.75/6.25	23.75/12.5	47.5/12.5	95/12.5

III. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor-blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium.

Metoprolol and hydrochlorothiazide have been used individually and in combination for the treatment of hypertension. The antihypertensive effects of these agents are additive.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

The mechanism of the antihypertensive effect of thiazide is unknown.

Dutoprol is indicated for the management of hypertension. The fixed-dose combination is not indicated for initial therapy

D. WHAT ARE THE PROPOSED DOSAGES AND ROUTE OF ADMINISTRATION?

Dosing must be individualized considering baseline and target blood pressure as well as experience with individual agents. In the clinical trial ATTACH where the combination was taken, the effective oral doses for HCT where 6.25 mg to 25 mg and for metoprolol succinate extended release the doses were 25 to 200 mg. The antihypertensive effects were additive when combined. Once an initial starting dose has been established, the initial response to treatment should be apparent within 2 weeks. Titration may be carried out every 2 weeks up to a maximum of 200/25 mg (two Dutoprol 100/12.5 mg tablets) administered once daily.

Metoprolol succinate extended release doses greater than 400 mg have not been studied. Patients usually do not require hydrochlorothiazide doses in excess of 50 mg daily when used in combination with other antihypertensive agents.

II. GENERAL CLINICAL PHARMACOLOGY

A. WHAT ARE THE DESIGN FEATURES OF THE CLINICAL PHARMACOLOGY AND THE CLINICAL STUDIES USED TO SUPPORT DOSING OR CLAIMS?

A total of eight studies were submitted, of which three (S-895, S-896, S-897) used a former formulation. However, the studies were reviewed due to pharmacokinetic supportive information. Study 324 was not reviewed from the CPB perspective since no pharmacokinetic objectives were addressed. Below are listed all submissions in the application.

Study	Objectives	Design	Subjects	Duration of treatment
S-895	Determine: 1) relative oral BA of MET as fixed combination of MET CR 100 mg + HCT 12.5 mg and as MET CR 100 mg alone; and 2) relative oral BA of HCT as fixed combination of MET CR 100 mg + HCT 12.5 mg as a HCT 12.5 mg tablet and as Esidrex® 25 mg tablet	Steady-state, randomized, open-label, 4-way cross-over, BA, fed	12 healthy male volunteers	20 days
S-896	Evaluate: 1) relative oral BA of MET and HCT in new CR combination compared with the conventional combination and 2)	Steady-state, randomized, double-blind, 3-way cross-	12 healthy male volunteers	15 days

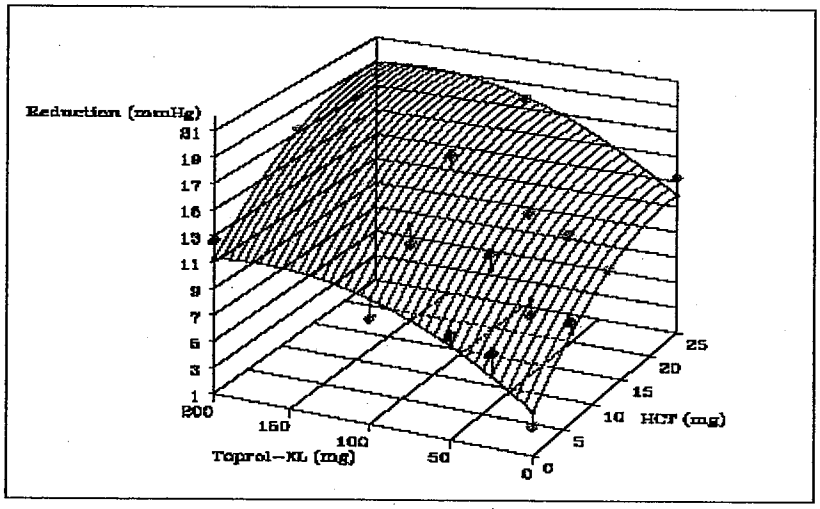
Study	Objectives	Design	Subjects	Duration of treatment
S-896 (cont.)	effect on exercise tachycardia in relation to placebo after administration of the two different combination tablets	over, PK/PD, fasted		
S-897	Evaluate: 1) extent and rate of absorption of MET in a fixed combination MET CR/HCT 50/12.5 mg and as MET CR 50 mg alone, and 2) extent and rate of absorption of HCT in the same fixed combination and as 12.5 mg of HCT alone	Steady-state, randomized, open-label, 3-way cross-over, fasted	12 healthy male volunteers	15 days
S-998	Determine whether a modified formulation of a fixed combination of MET CR 100 mg + HCT 12.5 mg (investigational/test) is BE to the marketed formulation of MET CR 100 mg + HCT 12.5 mg (reference)	Steady-state, randomized, open-label, 2-way cross-over, fasted	30 healthy male volunteers	14 days
D4026 C00005	Determine whether the fixed combination tablet (test) and the free combination (reference) of MET CR (1 X 100mg) and HCT (1 X 12.5 mg) tablets are BE under fed and fasted conditions	Single-dose, randomized, open-label, 4-way cross-over, fed and fasted	48 healthy volunteers 27M/21F	4 days
D4026 C00006	Determine whether the fixed combination tablet (2 test tablets) and the free combination (reference) of MET CR (2 X 50mg) and HCT (2 X 6.25 mg) tablets are BE under fasted conditions	Single-dose, randomized, open-label, 2-way cross-over, fasted	44 healthy volunteers 26M/18F	2 days
S-902	Compare the effects on BP and HR 24 hours after administration of the new combination product (MET CR 100 mg + HCT 12.5 mg) with that of the conventional combination (MET 100 mg + HCT 12.5 mg) in patients with essential HTN. Investigate the tolerability of both formulations.	Multiple-dose randomized, double-blind, 2-way cross-over. Double-blind period preceded by single-blind run-in 4-week period w/HCT 12.5 mg	48 patients (35M/13F) who remained hypertensive after the one-week run-in period	8 weeks total w/combination treatment
D4026 C00001 Study 324 (ATTACH)	Determine if combination of Toprol XL and HCT exceeds the BP lowering effects of each of its individual components w/regard to the placebo-corrected change from baseline to week 8 in trough SiDBP in hypertensive adults. Determine if the combination exceeds the contribution of each component in SiDBP, describe dose-response, compare each combination to its components, to placebo, examine same objectives for Standing DBP, and describe dose-response across sub-groups.	Multiple-dose, multiple-center, double-blind, placebo-controlled, parallel-group, unbalanced, factorial design	1571 patients	8 weeks to one of 17 treatments arms

B. WHAT IS THE BASIS FOR SELECTING THE RESPONSE ENDPOINTS AND HOW ARE THEY MEASURED IN CLINICAL PHARMACOLOGY STUDIES?

The major endpoints in study S-896 were effect on exercise tachycardia. In study S-902 the endpoints included supine DBP and HR with the measure of effect being the change from baseline 24 hours after drug administration. In study 324 (ATTACH) trough and peak standing and sitting DBP and SBP were the measured endpoints with regard to place-corrected change from baseline to week 8.

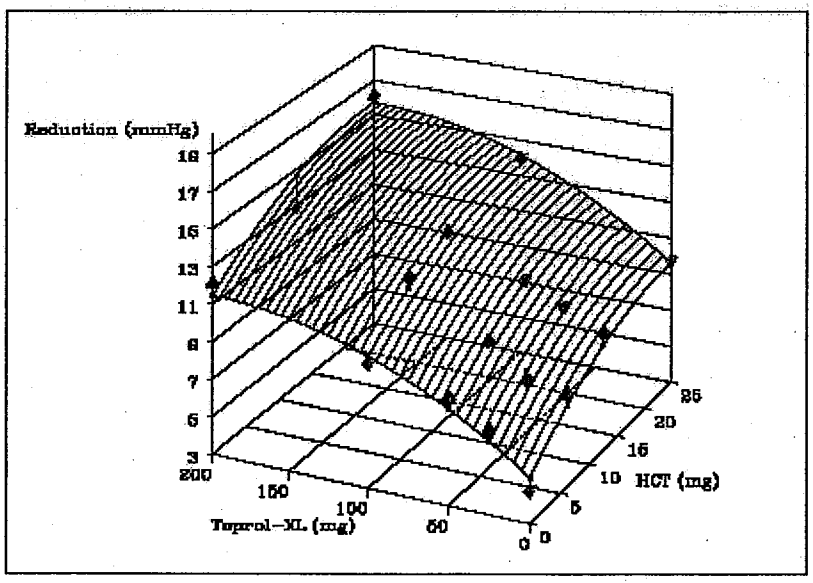
C. WHAT ARE THE CHARACTERISTICS OF THE EXPOSURE-RESPONSE RELATIONSHIPS FOR EFFICACY?

A dose-related blood pressure lowering effect was observed across the two clinical studies (studies 324 and S-902). Study 324 was a dose ranging study in the targeted population using a factorial design to explore dosing. ANCOVA analysis demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. The four treatment combinations of Toprol XL/HCT 100/6.25mg, 100/12.5mg, 100/25mg, and 200/25mg had significantly greater reductions than both of their respective components at significance level of <0.05. Below is a dose-response surface from the final polynomial regression analysis demonstrating changes in BP from baseline to week 8 LOCF in trough SiSBP and SiDBP, respectively in the ITT population. The individual components were administered together in this study and later studies D4026C00005 and D4026C00006 were conducted to demonstrate BE between the individual components administered together and the "to be marketed" formulation.



Note: Pyramids represent the treatment group mean values. Upward pyramids are above the surface, and downward pyramids are below the surface. Lines connect the pyramids with the corresponding fitted value on the regression surface.

Regression equation: SBP: y = –4.20691 –0.08645*Toprol-XL –0.63844*HCT + 0.00026*Toprol-XL2 + 0.01324*HCT2.



Note: Pyramids represent the treatment group mean values. Upward pyramids are above the surface, and downward pyramids are below the surface. Lines connect the pyramids with the corresponding fitted value on the regression surface.

Regression equation: DBP: $y = -5.34392 - 0.06023*\text{Toprol-XL} - 0.34772*\text{HCT} + 0.00015*\text{Toprol-XL}^2 + 0.00703*\text{HCT}^2$.

In study S-902, two combinations of metoprolol were studied (metoprolol succinate ER/HCT 100/12.5mg and conventional metoprolol tartrate IR/HCT 100/12.5mg. This study also had a run-in period where HCT 12.5mg once daily was administered. The MET CR/HCT dose selected for this trial was the only combination dose level available at the time of the study and was approved only outside the U.S.

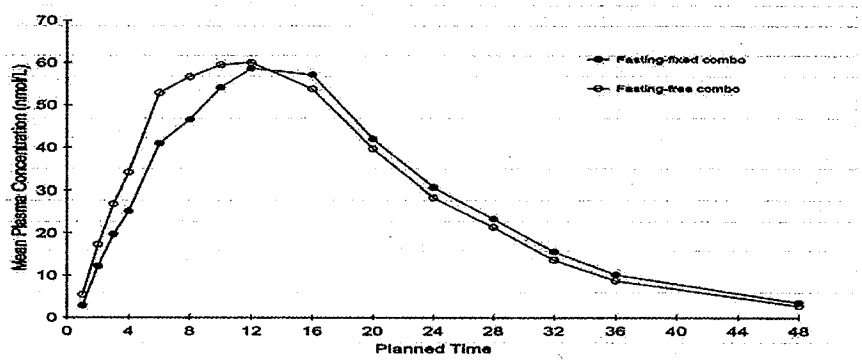
D. DOES DUTOPROL HAVE AN IMPACT ON QT/QTC INTERVAL?

A study measuring the impact of this product on the QTc interval in humans was not conducted.

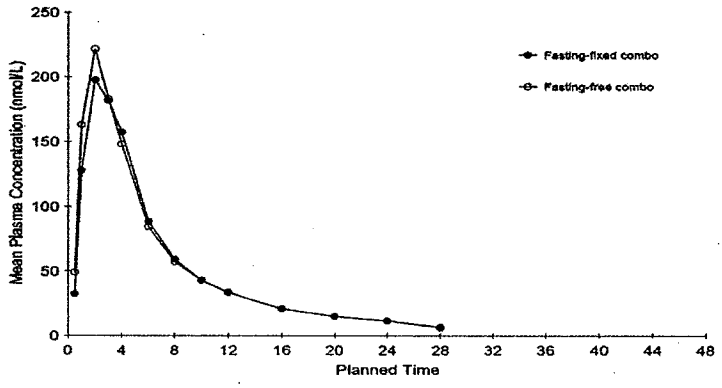
E. DOES THE EXPOSURE-RESPONSE DATA SUPPORT THE PROPOSED DOSING REGIMEN?

Once daily dosing is supported by study 324 clinical trial findings (peak:trough BP ratio close to 1.0 between baseline and week 8). The clinical trial findings supporting once daily dosing are also consistent with the 24-hour pharmacokinetic and pharmacodynamic profiles of the individual agents and the combination found in other pharmacokinetic studies.

Mean MET plasma concentration-time-curves for the fixed and free combination tablet strength of MET CR/HCT tablet 23.75/6.25mg (administered as two tablets from study D4026C00006) is depicted below:



Mean HCT plasma concentration-time-curves for the fixed and free combination tablet strength of MET CR/HCT tablet 23.75/6.25mg (administered as two tablets from study D4026C00006) is depicted below:



In study S-902 the effect on BP and HR 24 hours post dose of the new combination versus the conventional combination of metoprolol 100 mg and HCT 12.5 mg in patients with essential hypertension resulted in similar beta-blockade. However, the assessment of sufficient BP and HR being controlled at the end of the 24-hour dosing period was formally not addressed.

F. WERE ANY DRUG INTERACTIONS EXPLORED?

A drug interaction study was performed between metoprolol and HCT at steady state in study S-895 resulting in a decrease in metoprolol C_{max} of 23% when metoprolol succinate was administered with HCT (249 versus 191 nmol/L alone versus with HCT). T_{max}, C_{min} and AUC remained unchanged. HCT C_{max} was also affected by the addition of metoprolol resulting in a decrease of about 16% when coadministered (331 versus 279 nmol/L). T_{max}, C_{min} and AUC remained unchanged. Both changes are of no clinical significance.

III. GENERAL BIOPHARMACEUTICS

A. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS THE CLINICAL PHARMACOLOGY?

Both metoprolol and HCT were identified and measured in all studies except S-902. In this study only metoprolol trough concentrations were measured.

B. ARE THE PHARMACOKINETIC PARAMETERS FOR THE MET CR COMPONENT CONSISTENT FOR A CONTROLLED RELEASE FORMULATION?

In Study S-902, the plasma concentration of metoprolol, 24 hours after administration of the new combination product of metoprolol CR 100 mg and HCT 12.5 mg with that of the conventional combination of metoprolol conventional tablets 100 mg and HCT 12.5 mg in patients with essential hypertension was investigated resulting in higher sustained mean trough concentrations of metoprolol with the new fixed formulation when compared to the conventional formulation. The sponsor did not submit graphs even after being requested by the reviewer. The sponsor measured metoprolol concentrations strictly as a compliance method and stated that this analysis was not meant to be an indication of any claims with the new formulation.

Descriptive Statistics for Metoprolol Plasma Concentrations (nmol/L), All Available Data

		Met CR + HCT	Met Conv + HCT
Plasma concentration	N	46	47
	Mean	95.9	40.6
	SD	103.3	64.1
	Minimum	0.0	0.0
	Median	56.0	8.0
	Maximum	453.0	260.0

In study D4026C00005 and D4026C00006 bioequivalence was established between Toprol XL and the metoprolol succinate extended-release component of Dutoprol.

C. WAS AN ADEQUATE LINK ESTABLISHED BETWEEN THE CLINICAL AND TO-BE-MARKETED FORMULATIONS?

The sponsor conducted their Phase III clinical trial (Study 324 – ATACH) with the individual components administered together. As a result, bioequivalence between the clinical trial formulation and the to-be-marketed formulations is required. Since the different strengths of the "to-be-marketed" formulations are not compositionally proportional, two bioequivalence studies (D4026C00005 and D4026C00006) were performed involving the highest and lowest strength (MET CR/HCT 100/12.5mg and 25/6.25mg, respectively) with the intent to request a biowaiver for the two intermediate strengths (25/12.5mg and 50/12.5mg, respectively).

Study D4026C00005 was a single-dose, randomized, open-label, 4-way cross-over, fed and fasted study in 48 healthy volunteers with the highest strength (MET CR/HCT 100/12.5mg). Results below for metoprolol and HCT seem to indicate bioequivalence between the clinical trial formulation and the marketed formulation:

Metoprolol bioequivalence results:

	$AUC_{0-\infty}$[a]			
			90% CI	
	Ratio	Estimate	Lower	Upper
Primary				
C_{max} (nmol/L)	Fixed/Free combination, fasting	1.10	1.03	1.18
AUC_{0-t} (nmol*h/L)	Fixed/Free combination, fasting	0.99	0.94	1.05
$AUC_{0-\infty}$ (nmol*h/L)	Fixed/Free combination, fasting	0.99	0.94	1.05
Secondary				
C_{max} (nmol/L)	Fixed/Free combination, fed	1.06	0.99	1.14
AUC_{0-t} (nmol*h/L)	Fixed/Free combination, fed	0.98	0.93	1.04
$AUC_{0-\infty}$ (nmol*h/L)	Fixed/Free combination, fed	0.98	0.93	1.03
C_{max} (nmol/L)	Fed/Fasting, Fixed combination	1.04	0.97	1.11
AUC_{0-t} (nmol*h/L)	Fed/Fasting, Fixed combination	1.01	0.96	1.06
$AUC_{0-\infty}$ (nmol*h/L)	Fed/Fasting, Fixed combination	1.01	0.96	1.06
C_{max} (nmol/L)	Fed/Fasting, Free combination	1.08	1.01	1.16
AUC_{0-t} (nmol*h/L)	Fed/Fasting, Free combination	1.02	0.96	1.07
$AUC_{0-\infty}$ (nmol*h/L)	Fed/Fasting, Free combination	1.03	0.97	1.08

[a] Values were excluded for AUC_{0-t} (fasting-fixed: Subject Nos. 6 and 48, fasting-free: Subject No. 5, fed-free: Subject No. 9, fed-fixed: Subject No. 10) and $AUC_{0-\infty}$ (fasting-fixed: Subject No. 48) due to missing samples. The reason for exclusion was low precision ($AUC_{0-\infty}$, extrapolated area >20% of the total area) or possible underestimation (AUC_{0-t}).

HCT bioequivalence results:

	$AUC_{0-\infty}$[a]			
			90% CI	
	Ratio	Estimate	Lower	Upper
Primary				
C_{max} (nmol/L)	Fixed/Free combination, fasting	1.07	1.01	1.14
AUC_{0-t} (nmol*h/L)	Fixed/Free combination, fasting	1.04	1.00	1.08
$AUC_{0-\infty}$ (nmol*h/L)	Fixed/Free combination, fasting	1.04	1.00	1.08
Secondary				
C_{max} (nmol/L)	Fixed/Free combination, fed	0.96	0.91	1.02
AUC_{0-t} (nmol*h/L)	Fixed/Free combination, fed	0.98	0.94	1.03
$AUC_{0-\infty}$ (nmol*h/L)	Fixed/Free combination, fed	0.99	0.95	1.03
C_{max} (nmol/L)	Fed/Fasting, Fixed combination	0.87	0.82	0.92
AUC_{0-t} (nmol*h/L)	Fed/Fasting, Fixed combination	0.94	0.90	0.98
$AUC_{0-\infty}$ (nmol*h/L)	Fed/Fasting, Fixed combination	0.94	0.90	0.98
C_{max} (nmol/L)	Fed/Fasting, Free combination	0.97	0.92	1.03
AUC_{0-t} (nmol*h/L)	Fed/Fasting, Free combination	0.99	0.95	1.03
$AUC_{0-\infty}$ (nmol*h/L)	Fed/Fasting, Free combination	0.99	0.95	1.03

[a] Values were excluded due to missing samples for AUC_{0-t}, i.e., possible underestimation (fasting-fixed: Subject Nos. 6 and 48, fasting-free: Subject No. 5) and due to low precision in the estimation of $AUC_{0-\infty}$, extrapolated area >20% of total area, (fasting-fixed: Subject No. 5, fasting-free: Subject No. 5, fed-free: Subject No. 5) or low Rsq adjusted for the λ_z estimation (fed-free: Subject No. 3).

In study D4026C00006, bioequivalence was evaluated with the lowest MET CR/HCT combination (fixed or free combination) of 25/6.25mg (given as 2 X 25 mg/6.25 mg). This was a single-dose, randomized, open-label, 2-way cross-over, fasted study in 44 healthy volunteers. Metoprolol C_{max} 90% CI was 84 to 97%, while the CI for AUC_{0-t} was 94 to 105% and for $AUC_{0-\infty}$ 94 to 105% as well. HCT also demonstrated bioequivalent with regard to C_{max} (90% CI 88 to 99%), AUC_{0-t} (93 to 103% CI), and $AUC_{0-\infty}$ (93 to 103%).

D. CAN A BIOWAIVER BE GRANTED FOR THE INTERMIDEATE STRENGTHS?

Metoprolol

All fixed combination strengths demonstrated F_2 similarity comparison against the reference.

Metoprolol in-vitro dissolution profile comparisons of fixed combinations and monotherapy tablets by F_2 similarity test

Tablets Test	Tablets Reference	pH 1.2	pH 4.0	pH 6.8	pH7.5
23.75+12.5mg	23.75+6.25mg	83	89	84	77
47.5+12.5mg	95/12.5mg	84	59	65	63

HCT

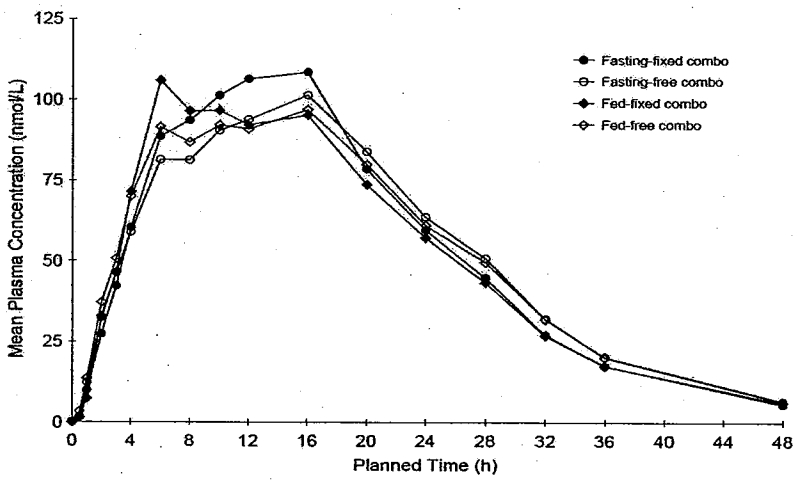
The clinical trial formulation of HCT for study 324 had been developed by the sponsor specifically for that trial. The sponsor is requesting that no F_2 similarity comparison be made since a very rapid dissolution was observed (_____ minutes) in all media tested.

A waiver for further biostudies of the intermediate strengths is granted due to demonstration of similarity through the F2 similarity comparison for the metoprolol component and rapid dissolution of the HCT component in all media tested (NLT ____ in ___ minutes.

E. WHAT IS THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF THE DRUG FROM THE DOSAGE FORM?

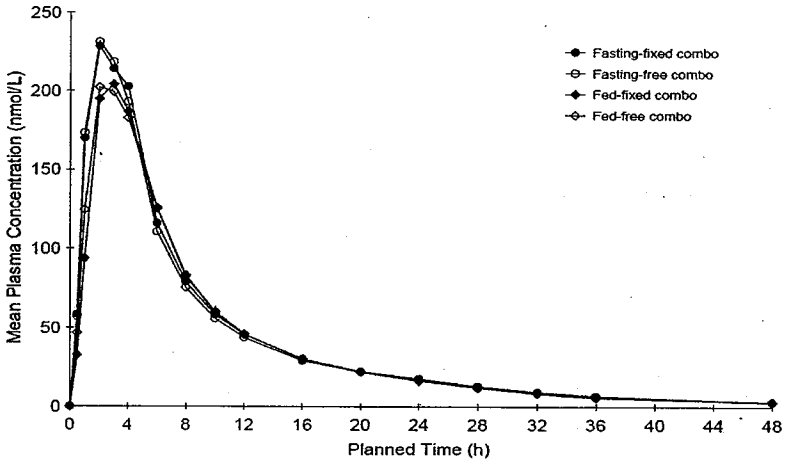
As demonstrated in study D4026C00005, food had little impact on the rate and extent of absorption of Dutoprol. Metoprolol C_{max} fasted versus fed was 121 and 118 nmol/L, respectively with a CV% of 87 and 75.1%. T_{max} was 10.38 versus 8.15 hours (fasted to fed) with a CV% of 35.7 and 54.3%. AUC_{0-t} was 2440 versus 2362 nmol·h/L with a CV% 97.5 and 91.7%. $AUC_{0-\infty}$ was 2583 versus 2505 nmol·h/L with a CV% of 97.8 and 92.4%. All pharmacokinetic variables had a high CV%. As a result, the clinical impact of the variability would be negligible.

Study results for D4026C0005 (Metoprolol succinate extended-release 100 mg) – mean plasma concentration versus time curves:



For **HCT** - C_{max} pharmacokinetic variables were different but not clinically relevant since the difference was about 14%. The CV% was not as high as observed for the metoprolol component of the fixed tablet formulation. There was less disparity in AUC parameters for HCT fixed combination. T_{max} differences were small as well and not of any clinical significance.

HCT mean plasma concentration time profiles for each treatment is shown below under fed and fasted state:



Variable	Statistics	Fasting		Fed	
		Fixed combination	Free combination	Fixed combination	Free combination
C_{max}	N	48	48	48	47
(nmol/L)	Mean	268	254	231	241
	SD	76.6	81.7	53.2	56.5
	Median	250	243	223	231
	Range	161-471	80.9-444	119-390	109-385
	CV%	28.6	32.2	23.0	23.4
t_{max}	N	48	48	48	47

Variable	Statistics	Fasting		Fed	
		Fixed combination	Free combination	Fixed combination	Free combination
(h)	Mean	2.44	2.45	2.84	2.62
	SD	1.13	0.92	0.98	1.08
	Median	2.00	2.03	3.00	2.00
	Range	1.00-4.17	0.50-4.00	1.00-6.00	1.00-6.02
	CV%	46.2	37.4	34.4	41.1
AUC_{tz}	N	46	47	48	47
(nmol*h/L)	Mean	1941	1891	1869	1844
	SD	454	511	370	352
	Median	1942	1916	1845	1805
	Range	1159-3337	628-3319	917-2832	1171-3026
	CV%	23.4	27.0	20.5	19.1
AUC_{∞}	N	47	47	48	45
(nmol*h/L)	Mean	2046	1990	1920	1957
	SD	473	515	390	368
	Median	2014	2020	1921	1904
	Range	1203-3432	742-3386	981-2963	1241-3128
	CV%	23.1	25.9	20.3	18.5
$t_{1/2}$	N	48	48	48	46
(h)	Mean	10.2	9.77	9.63	9.84
	SD	3.76	3.05	3.87	4.01
	Median	9.06	9.09	8.42	8.90
	Range	6.67-28.0	5.65-24.0	6.14-25.1	6.04-29.6
	CV%	36.8	31.2	40.2	40.7
λ_z	N	48	48	48	46
	Mean	0.0739	0.0755	0.0798	0.0772
	SD	0.0185	0.0167	0.0200	0.0192
	Median	0.0765	0.0762	0.0833	0.0780

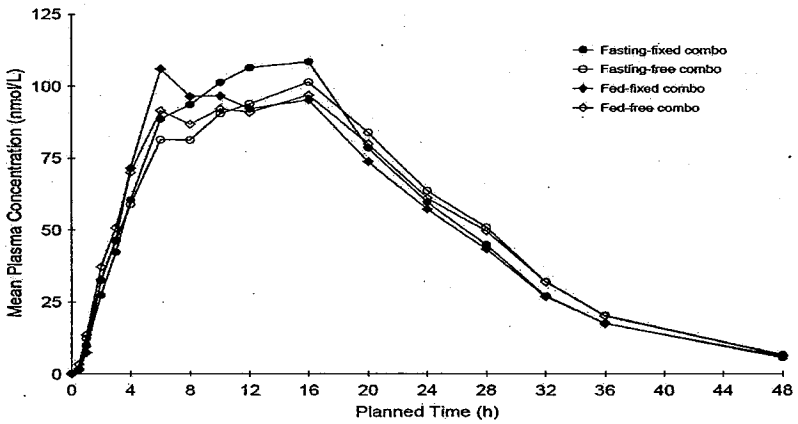
Variable	Statistics	Fasting		Fed	
		Fixed combination	Free combination	Fixed combination	Free combination
	Range	0.0248-0.104	0.0289-0.133	0.0276-0.113	0.0234-0.115
	CV%	25.0	22.2	25.2	24.9

F. DOES THE METOPROLOL CR COMPONENET OF THE DIFFERENT STRENGTHS OF DUTOPROL MEET THE CONTROLLED RELEASE CLAIMS FOR IT AND DOES THE PHARMACOKINETICS RULE OUT DOSE DUMPING?

In bioequivalence study D4026C0005, metoprolol succinate, the extended release component of Dutoprol was evaluated for bioequivalence against Toprol XL (metoprolol succinate extended release marketed by the sponsor and used in the Phase III clinical trial). The concentration versus time curve of both formulations is shown

below demonstrating almost superimposable time course for concentrations by treatment.

Study results for D4026C0005 (Metoprolol CR 100 mg) – mean plasma concentration versus time curves:

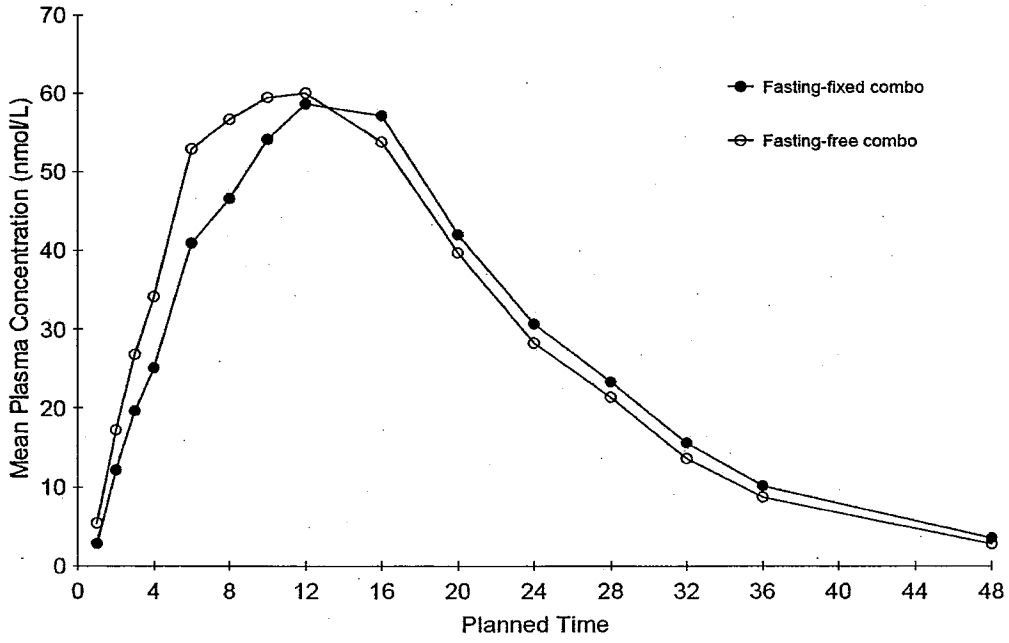


Below are metoprolol pharmacokinetic summary descriptive statistics (from study D4026C00005) after treatment with a single dose of the fixed combination tablet and the free combination of metoprolol succinate and HCT in the fasted and fed state (MET CR 100mg/HCT 12.5 mg).

Variable	Statistics	Fasting		Fed	
		Fixed combination	Free combination	Fixed combination	Free combination
C_{max}	N	48	48	48	47
(nmol/L)	Mean	121	108	118	114
	SD	105	87.8	88.6	93.7
	Median	89.8	81.2	85.4	74.6
	Range	27.4-512	19.2-421	23.8-427	24.1-458
	CV%	87.0	81.0	75.1	82.0
t_{max}	N	48	48	48	47
(h)	Mean	10.38	13.09	8.15	9.88
	SD	3.71	4.33	4.42	4.90
	Median	10.00	16.00	6.00	8.00
	Range	4.00-16.05	6.00-20.00	2.00-20.03	3.00-20.00
	CV%	35.7	33.1	54.3	49.6
AUC_{0-t}	N	46	47	47	46
(nmol*h/L)	Mean	2440	2538	2362	2345
	SD	2379	2335	2166	2151
	Median	1706	1849	1597	1573
	Range	541-11432	437-11277	488-10346	533-10853
	CV%	97.5	92.0	91.7	91.7
$AUC_{0-\infty}$	N	47	48	48	47
(nmol*h/L)	Mean	2583	2569	2505	2580
	SD	2528	2462	2315	2498
	Median	1722	1839	1672	1746
	Range	545-12293	458-12297	498-11216	536-11548

Variable	Statistics	Fasting		Fed	
		Fixed combination	Free combination	Fixed combination	Free combination
	CV%	97.8	95.9	92.4	96.8
$t_{1/2}$	N	48	48	48	47
(h)	Mean	6.44	6.54	6.95	6.92
	SD	1.20	1.32	1.58	1.15
	Median	6.33	6.49	6.89	7.11
	Range	3.26-9.97	3.48-10.6	4.02-12.6	4.87-9.61
	CV%	18.6	20.2	22.7	16.6
λ_z	N	48	48	48	47
	Mean	0.112	0.110	0.104	0.103
	SD	0.0232	0.0233	0.0221	0.0179
	Median	0.110	0.107	0.101	0.0974
	Range	0.0696-0.213	0.0653-0.199	0.0551-0.173	0.0721-0.142
	CV%	20.8	21.1	21.1	17.4

Metoprolol results from Study D4026C00006 where the individual components and fixed combination of MET CR/HCT 25/6.25 mg were administered as a single dose under fasted conditions:



Metoprolol summary statistics of pharmacokinetic variables of both the fixed and free combination:

Variable	Statistics	Fixed combination	Free combination
C_{max}	N	42	43
(nmol/L)	Mean	63.2	67.6
	SD	62.9	63.7
	Median	35.6	44.7
	Range	11.5, 257	15.8, 264
	CV%	99.5	94.3
	Geometric mean	43.8	48.6
t_{max}	N	42	43
(h)	Mean	11.87	9.91
	SD	3.17	2.93
	Median	12.00	10.00
	Range	6.00, 16.05	5.98, 16.02
	CV%	26.7	29.5
	Geometric mean	11.42	9.47
AUC_{0-t}	N	42	43
(nmol*h/L)	Mean	1307	1327
	SD	1466	1551
	Median	649	691
	Range	245, 5371	213, 6546
	CV%	112.1	116.8
	Geometric mean	848	854
$AUC_{0-\infty}$	N	42	43
(nmol*h/L)	Mean	1359	1368
	SD	1576	1632
	Median	656	695
	Range	251, 5718	220, 6786
	CV%	116.0	119.3
	Geometric mean	866	873
$t_{1/2}$	N	42	43
(h)	Mean	6.31	5.61
	SD	1.71	1.47
	Median	6.19	5.36
	Range	4.15, 15.1	3.45, 11.8
	CV%	27.1	26.1
	Geometric mean	6.14	5.46
λ_z	N	42	43
(1/h)	Mean	0.115	0.130
	SD	0.0226	0.0282
	Median	0.112	0.129
	Range	0.0458, 0.167	0.0587, 0.201
	CV%	19.6	21.6
	Geometric mean	0.113	0.127

G. Does the pharmacokinetics of the metoprolol CR componenet of the different strengths of Dutoprol rule out dose dumping?

The lack of dose dumping by the new formulation in comparison to the Toprol XL formulation is demonstrated in the figures above for studies D4026C00005 and 00006.

H. What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

Both components of Dutoprol demonstrated bioequivalence in relation to the clinical trial formulation as depicted above. As a result, it would be expected that the rate and extent of absorption of both components of Dutoprol would be the same as their individual counterparts. Point estimates for the fixed in relation to the free combination for metoprolol (100/12..5 mg strength) was 0.99 under fasted conditions and 0.98 under

fed conditions. Point estimates for HCT (same strength) were 1.04 for fasted versus 0.99 under fed conditions. Both studies were single dose studies. No steady state bioavailability data is available for the highest strength.

I. ARE THE PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS ACCEPTABLE?
The dissolution methods and specifications proposed by the sponsor are different for the metoprolol succinate ER component and the HCT component.

For the **Metoprolol** component, all metoprolol succinate media data submitted by the sponsor is in 500 mL of sodium phosphate buffer solution pH 6.8, 37° C, using USP apparatus II at 50 and 75 rpm. All the data was dedicated to the justification of their chosen speed and specification proposal to the Agency. The sponsor's proposed dissolution methods and specifications for the **MET CR** component of Dutoprol is as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	75 rpm	
Medium	Sodium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT — of label claim
	After 4 hours	——— of label claim
	After 8 hours	of label claim
	After 20 hours	NLT ___ of label claim

USP recommendations for metoprolol succinate ER dissolution methods and specifications are as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	50 rpm	
Medium	Potassium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT 25% of label claim
	After 4 hours	20 to 40% of label claim
	After 8 hours	40 to 60% of label claim
	After 20 hours	NLT 80% of label claim

After reviewing all metoprolol succinate dissolution raw data:

- The proposed 20-hour time specification can be tightened-up to 18 hours since the dissolution profile seems to reach an asymptote by that time point and in order to allow for more discriminatory assessment for quality control purposes.

The dissolution method is acceptable; but not the proposed specifications for the metoprolol succinate ER component of Dutoprol. The Agency's specification recommendation is as follows:

Q	After 1 hour	NMT —— of label claim
	After 4 hours	—— of label claim
	After 8 hours	of label claim
	After 18 hours	NLT —— of label claim

All **HCT** dissolution media data submitted by the sponsor is according to USP methods for HCT (0.1N HCl). No other dissolution media was used in the development of the dissolution method for the HCT component of the new product. The media volume is different from the USP monogram —— instead of the recommended 900mL. All data submitted was dedicated to the justification of their chosen Apparatus, Speed, and Specification proposal to the Agency.

The sponsor's proposed dissolution methods and specifications for the **HCT** component of Dutoprol is as follows:

Apparatus	USP Apparatus ——
Speed	100 rpm
Medium	0.1 M HCl
Volume	——
Temperature	37° C ± 0.5° C
Q	NLT —— minutes

USP recommendations for HCT dissolution methods and specifications are as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT 80% in 60 minutes

In reviewing the submitted data for HCT and checking the "Guidance for Industry – Dissolution Testing of Immediate Release Solid Oral Dosage Forms":

1) According to the above mentioned guidance, "dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-minute intervals, to generate a dissolution profile". The sponsor's recommendation for Apparatus—— at a speed of 100 rpm is not a speed that is recommended by the guidance as being "mild test conditions" and is not a method that would be considered discriminatory enough. In addition, USP recommendation of Apparatus I at a speed of 100 rpm is part of the quality control dissolution test described in the USP and seems to provide adequate dissolution results according to the data submitted by the sponsor to include biowaiver data.

2) The new specifications of a Q of NLT —— minutes is not appropriate since it is evident from the raw data submitted that all units tested dissolved at a mean rate of —, or more within — minutes and is the basis for the sponsor not performing an F_2 similarity factor calculation for HCT for biowaiver purposes (see F_2 similarity Factor and Biowaiver section).

3) The volume utilized in all the biowaiver data submitted was 900 mL, not ——L. In order to align the dissolution methods and specifications with the data submitted to justify a biowaiver, the media volume for the dissolution method for HCT will be 900 mL.

As a result, the dissolution method and specifications for the HCT component of Dutoprol is as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT —— minutes

J. IS THE PROPOSED LABELING FOR DUTOPROL ACCEPTABLE?

The proposed labeling is acceptable provided the Reviewer Labeling Comments described in the Recommendations section are addressed by the sponsor. A copy of the proposed package insert is included in Appendix I.

IV. ASSAY AND VALIDATION

A. WERE ALL ASSAYS VALIDATED?

In studies D4026C00005 and D4026C00006 metoprolol plasma concentrations were assessed by LC-MS/MS method that was validated in the range of 0.5 to 600 nmol/L. In the same studies, HCT plasma concentrations were assessed by —— detection method and validated in the range of 0.5 to 600 nmol/L as well.

In study S-896, there were inconsistencies reported in the assay validation study results for both metoprolol and HCT leading to confusion on what the sponsor reported. As a results, a clear assessment of assay validation is not possible. However, since this study was submitted as a supportive study, the discrepancy in results are of less significance.

Study S-897 had missing HCT in urine assay methodology data. The reviewer brought this to the attention of the sponsor and they are unable to locate any study specific validation reports. As a result, the sponsor is proposing that the review of this study for HCT be based on the plasma data and no urine data.

Studies D4026C00005 and D4026C00006 had inconsistencies in how the HCT in plasma accuracy data for the percent recovered was reported. The report stated that the percent recovered ranged from 87 to 92% in a concentration range of 20 to 500 nmol/L. The sponsor did not provide recovery data for lower concentrations (down to 5 nmol/L) and higher concentrations (>500 up to 1000 nmol/L). Reports in Summary document 2.7.1 state that mean accuracy was 0.3 to 3.7%; but whether this was a CV% was not clear.

Study S-998 also had inconsistencies in how assay methodology was reported even after numerous requests by the reviewer to the sponsor. MET in plasma had inconsistencies

in the way linearity and accuracy were reported. HCT in plasma had inconsistencies in how the LLOQ was reported with two different reports with different findings. HCT in urine assay results had inconsistencies in how linearity and accuracy were reported.

As a result, a true assessment of assay methodology and validation in studies S896, S-897, and S-998 is not possible. Studies D4026C00005 and D4026C00006 had inconsistencies in how they reported the recovery of HCT in plasma because it was reported for a finite range and not the full linearity range they claim to have achieved with their assay. As a result, validation of HCT in plasma assay methodology is not possible.

DETAILED LABELING RECOMMENDATIONS

The following Labeling Recommendations should be addressed by the sponsor:

1. The following statement should be changed in the "PHARMACOKINETIC" section of the proposed label in order to align itself with findings in study D4026C00005:

Proposed by Sponsor:
Pharmacokinetics

Recommended by Agency:
Pharmacokinetics

The rate and extent of absorption of metoprolol/ hydrochlorothiazide are similar in the fasting state and after a high-fat meal when given as TRADE NAME tablets. (See DOSAGE AND ADMINISTRATION.)

Single dose pharmacokinetics of metoprolol/hydrochlorothiazide given as TRADE NAME tablets is similar to that of each drug given individually as Toprol XL® and a formulation of hydrochlorothiazide created for the clinical trial.

2. The following statement should be changed in the "PHARMACOKINETIC" section of the proposed label for better clarity:

Proposed by Sponsor:
Pharmacokinetics

Recommended by Agency:
Pharmacokinetics
Metoprolol succinate extended release component of

3. The following comment should be added to the "WARNING" section of the proposed label in order to direct the reader to the appropriate section corresponding to the dosage adjustment statement:

Proposed by Sponsor:
Hydrochlorothiazide

Recommended by Agency:
Hydrochlorothiazide
Renal Disease: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function *(see DOSAGE AND ADMINISTRATION).*

Hepatic Disease: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma *(see DOSAGE AND ADMINISTRATION).*

Hepatic Disease: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma *(see DOSAGE AND ADMINISTRATION).*

Appendix I:
Proposed Package Insert

19 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Appendix II:
Individual Review of Pharmacokinetic Studies

47 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

APPENDIX III
BIOWAIVER REQUEST

All dissolution data associated with the F_2 similarity factor assessment for **metoprolol** were performed using Apparatus 2 at 75 rpm. Media tested included pH 1.2, 4.0, 6.8 and 7.5 in a volume of 500 mL.

Metoprolol

The reference utilized by the sponsor to generate F_2 similarity data was incorrect (monotherapy used in study 324) since two bioequivalence studies were performed. One study was with the lowest (23.75/6.25 mg) and the other study with the highest (95/12.5 mg) strength to be marketed in order to obtain references by which to perform the F_2 similarity comparison with the intermediate strengths (23.75/12.5 mg and 47.5/12.5 mg) and for requesting the granting of a biowaiver of additional in-vivo studies. As a result, the reviewer generated her own F_2 similarity data from information contained in the data submitted. Results are depicted below:

Metoprolol in-vitro dissolution profile comparisons of fixed combinations and monotherapy tablets by F_2 similarity test

Tablets	Tablets				
Test	**Reference**	**pH 1.2**	**pH 4.0**	**pH 6.8**	**pH7.5**
23.75+12.5mg	23.75+6.25mg	83	89	84	77
47.5+12.5mg	95/12.5mg	84	59	65	63

Based on the data generated by the reviewer, similarity between the reference products and the intermediate strengths has been demonstrated for the metoprolol component of the fixed combination formulation.

HCT

The clinical trial formulation of HCT for study 324 had been developed by the sponsor specifically for that trial. The sponsor is suggesting that no F_2 similarity comparison is necessary since a very rapid dissolution was observed (> [redacted] minutes) using the method of USP apparatus [redacted] at 100 rpm. According to the "Guidance for Industry – Dissolution Testing of Immediate Release Solid Oral Dosage Forms", dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm. The test conditions used in this study report are not under "mild test conditions" since apparatus [redacted] is being utilized at 100 rpm not allowing for any discriminatory assessment. As a result, the sponsor was requested to perform F_2 similarity comparison calculations on HCT in all dissolution media before a biowaiver can be granted. Reference is made to the submission amendment made to the NDA on August 8, 2006 where additional data was submitted to justify the sponsor's claim of no need for a F_2 similarity comparison. All data submitted is summarized below:

Figure 1 **Mean (n=12) in vitro dissolution-time profiles of HCT at pH 1.2, USP 1 (basket), 100 rpm**

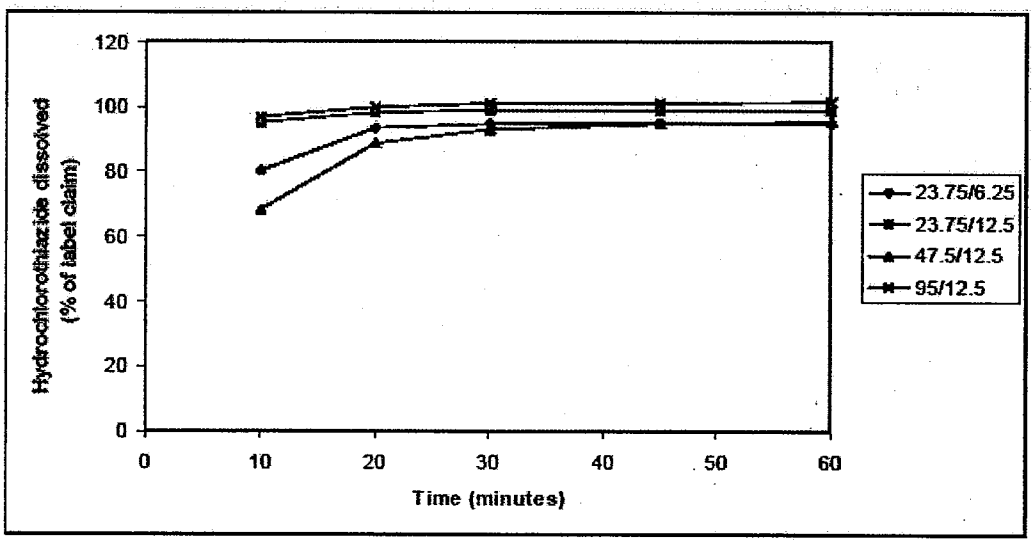


Figure 2 **Mean (n=12) in vitro dissolution-time profiles of HCT at pH 4.5, USP 1 (basket), 100 rpm**

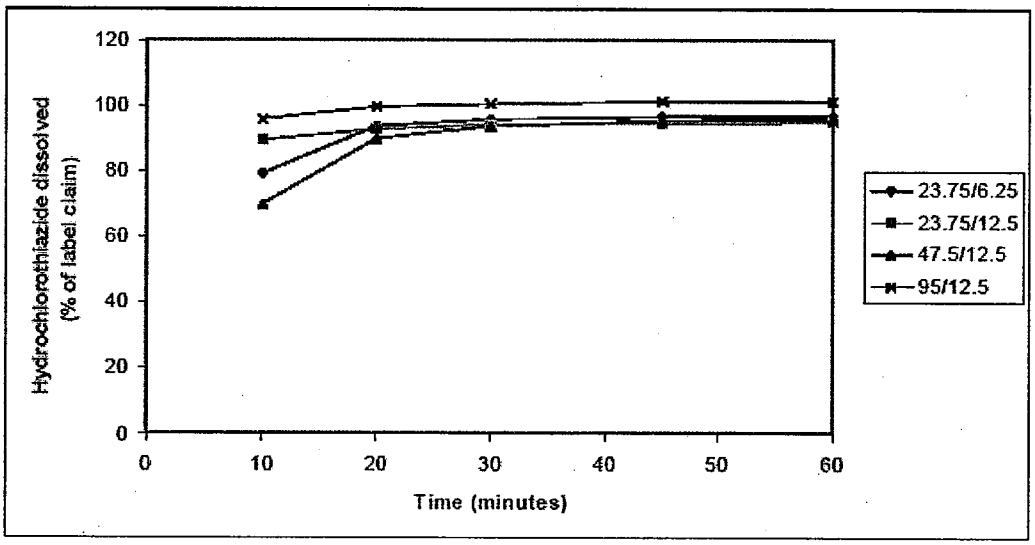
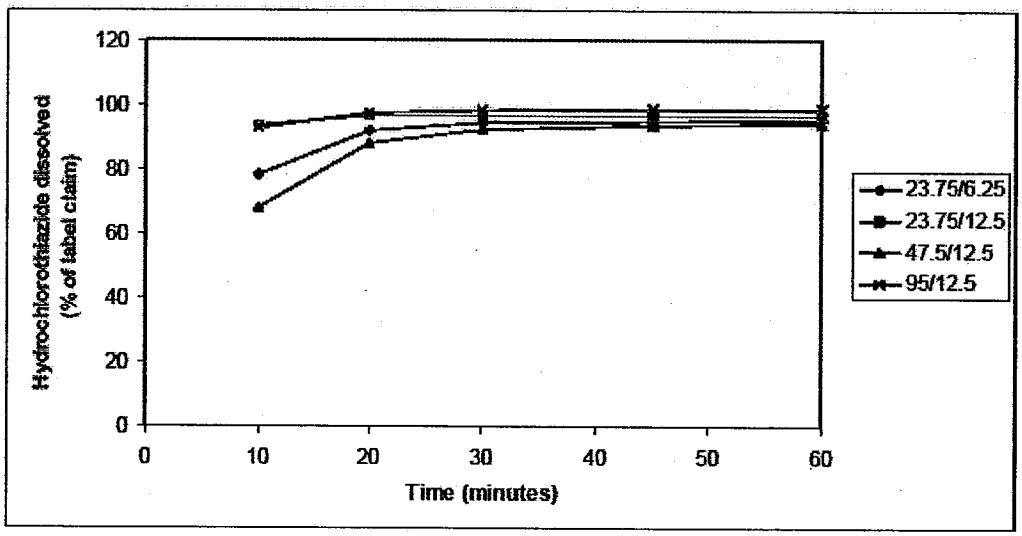


Figure 3 **Mean (n=12) in vitro dissolution-time profiles of HCT at pH 6.8, USP 1 (basket), 100 rpm**



The justification for not performing F_2 similarity comparisons with the HCT component of the fixed combination has been made.

Based on all data submitted for both Metoprolol and HCT, a waiver to conduct any additional in-vivo studies with the intermediate strengths for the purposes of demonstrating bioequivalence is granted.

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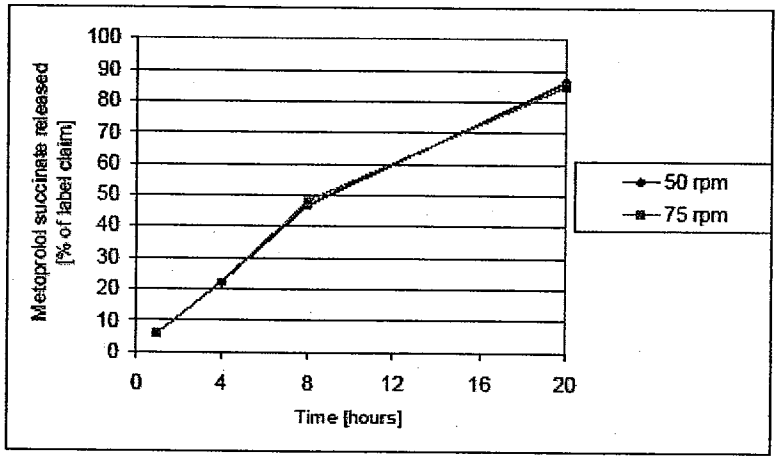
APPENDIX IV
DISSOLUTION

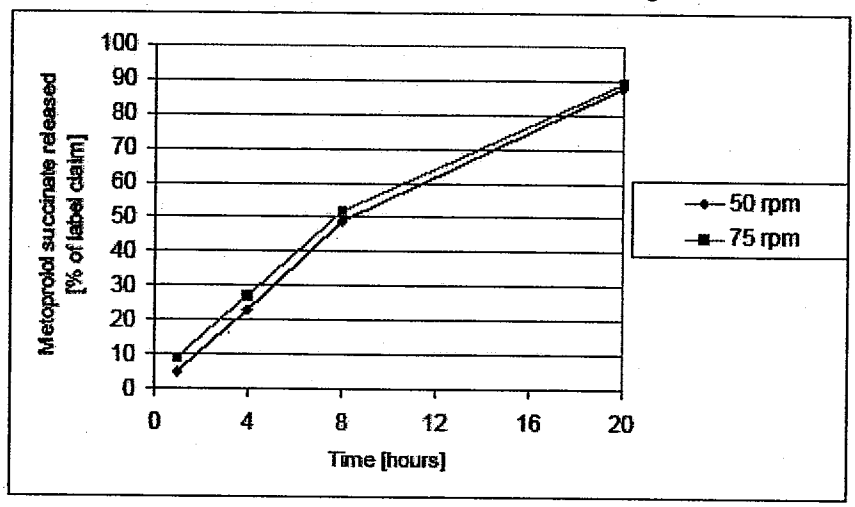
The sponsor is using a level A IVIVC that was developed for Toprol XL as their argument for establishing the dissolution specifications for the metoprolol component of the new formulation. The Agency has reminded the sponsor that they could not use the IVIVC developed for their existing product Toprol XL for Dutoprol since this is a new formulation. As a result, the dissolution methods and specifications for the metoprolol component of Dutoprol in this review will be approached without the aid of an IVIVC. In addition, the sponsor is proposing two different dissolution methods for Dutoprol (one for metoprolol and the other for HCT); which will be assessed individually by the reviewer.

All metoprolol succinate media data submitted by the sponsor is in 500 mL of phosphate buffer solution pH 6.8, 37° C, using USP apparatus II at 50 and 75 rpms. Graphs below will contain data for the 23.75/6.25mg strength in addition to all other strengths of the fixed combination product of Dutoprol; but the strength of 23.75/6.25mg is not intended for marketing. In addition, all data below is dedicated to the justification of their chosen Speed and Specification proposal to the Agency.

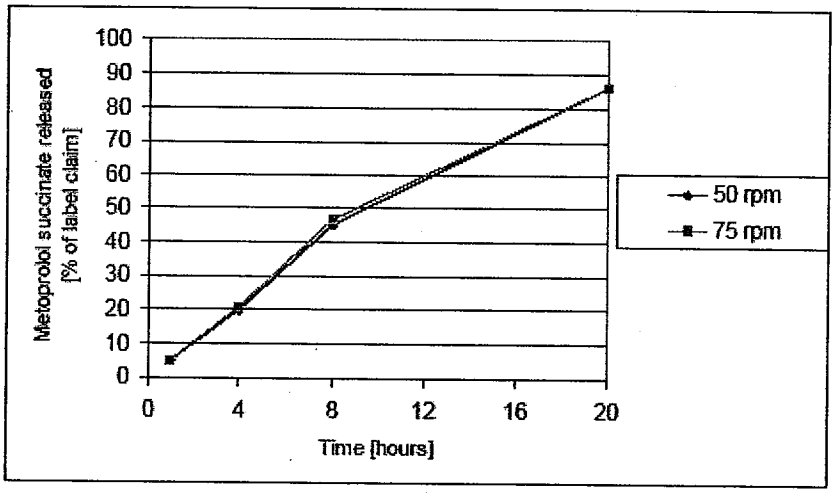
Mean drug release of metoprolol succinate from 23.75/6.25mg tablets – Batch No. H1699-01-01-02



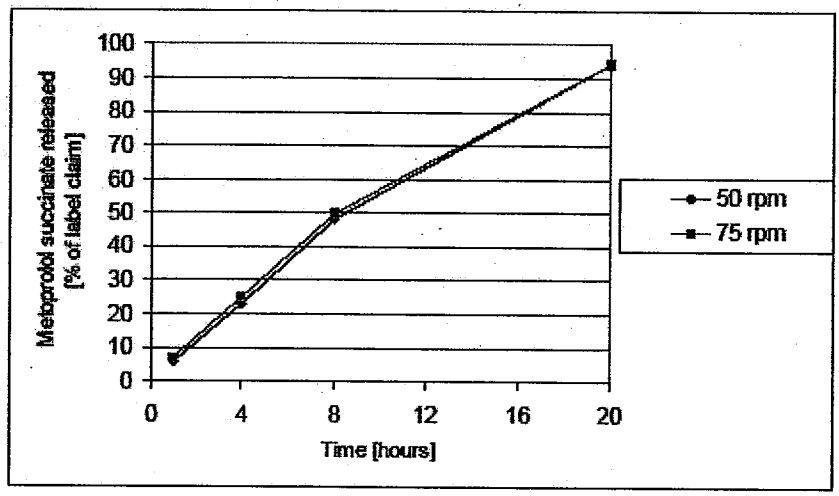
Mean drug release of metoprolol succinate from 23.75/12.5mg tablets – Batch No. H1764-01-01-01



Mean drug release of metoprolol succinate from 47.5/12.5mg tablets – Batch No. H1779-01-01-01



Mean drug release of metoprolol succinate from 95/12.5mg tablets – Batch No. H0712-07-02-02



The sponsor's proposed dissolution methods and specifications for the **MET CR** component of Dutoprol is as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	75 rpm	
Medium	Sodium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT ~~f~~ label claim
	After 4 hours	of label claim
	After 8 hours	of label claim
	After 20 hours	NLT of label claim

USP recommendations for metoprolol succinate ER dissolution methods and specifications are as follows:

Apparatus	USP Apparatus II (paddle)	
Speed	50 rpm	
Medium	Potassium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT 25% of label claim
	After 4 hours	20 to 40% of label claim
	After 8 hours	40 to 60% of label claim
	After 20 hours	NLT 80% of label claim

After reviewing all metoprolol succinate dissolution raw data:

- The proposed 20 hour time specification can be tightened-up to 18 hours since the dissolution profile seems to reach an asymptote by that time point and in order to allow for more discriminatory assessment for quality control purposes.

As a result, the dissolution method is acceptable. However, the specifications should be modified:

Apparatus	USP Apparatus II (paddle)	
Speed	75 rpm	
Medium	Sodium Phosphate Buffer Solution, pH 6.8	
Volume	500 mL	
Temperature	37° C ± 0.5° C	
Q	After 1 hour	NMT — of label claim
	After 4 hours	——— of label claim
	After 8 hours	of label claim
	After 18 hours	NLT — of label claim

All **HCT** dissolution media data submitted by the sponsor is according to USP methods for HCT (0.1N HCl). No other dissolution media was used in the development of the dissolution method for the HCT component of the new product. All data submitted was dedicated to the justification of their chosen Apparatus, Speed, and Specification proposal to the Agency as demonstrated below in the proposed dissolution methods. As a result, the reviewer utilized the dissolution information submitted for justification of no need for a F_2 similarity comparison to determine the appropriateness of their proposed dissolution methods and specifications; which is depicted in the Biowaiver section above.

The sponsor's proposed dissolution methods and specifications for the **HCT** component of Dutoprol is as follows:

Apparatus	USP Apparatus ———
Speed	100 rpm
Medium	0.1 M HCl
Volume	———
Temperature	37° C ± 0.5° C
Q	NLT ——— minutes

USP recommendations for HCT dissolution methods and specifications are as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT 80% in 60 minutes

In reviewing the submitted data and checking the "Guidance for Industry – Dissolution Testing of Immediate Release Solid Oral Dosage Forms":

1) According to the above mentioned guidance, "dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-minute intervals, to generate a dissolution profile". The sponsor's

recommendation for Apparatus —— t a speed of 100 rpm is not a speed that is recommended by the guidance as being "mild test conditions" and is not a method that would be considered discriminatory enough. In addition, USP recommendation of Apparatus I at a speed of 100 rpm is part of the quality control dissolution test described in the USP and seems to provide adequate dissolution results according to the data submitted by the sponsor.

2) The new specifications of a Q of NLT —— minutes is not appropriate since it is evident from the raw data submitted that all units tested dissolved at a rate of — or more within — minutes and is the basis for the sponsor not performing an F_2 similarity factor calculation for HCT for biowaiver purposes (see F_2 similarity Factor and Biowaiver section).

3) The dissolution media volume used for the justification that no F_2 similarity factor calculation for HCT be made was 900 mL, not the proposed ——

As a result, the dissolution method and specifications for the HCT component of Dutoprol is as follows:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Medium	0.1 M HCl
Volume	900 mL
Temperature	37° C ± 0.5° C
Q	NLT — minutes

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Appendix V
COVER SHEET AND OCPB FILING/REVIEW FORM

6.1.1. Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-956	Brand Name	Dutoprol
OCPB Division (I, II, III)	DPE 1	Generic Name	Metoprolol Succinate ER/Hydrochlorothiazide
Medical Division	HFD-110	Drug Class	Beta Blocker/Diuretic
OCPB Reviewer	Lydia Velazquez	Indication(s)	Hypertension
OCPB Team Leader	Patrick Marroum	Dosage Form	Tablets – 25/12.5 mg, 50/12.5 mg, 100/12.5 mg (metoprolol/hydrochlorothiaze, respectively)
		Dosing Regimen	QD
Date of Submission	28 October 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	July 2006	Sponsor	AstraZeneca, Inc.
PDUFA Due Date		Priority Classification	S4
Division Due Date	June 2005		

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	8		6 PK and 2 Efficacy
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
6.2 Healthy Volunteers-				
single dose:	X	2		Two BE studies for 25/6.25 mg and 100/12.5 mg strengths
multiple dose:	X	4		2 BA, 1 PK/PD, and 1 BE at SS
6.2.1. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	2		
solution as reference:				
alternate formulation as reference:	X	2		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				**Data missing**
(IVIVC):	X			**TBD if can be incorporated for Metoprolol ER**
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		**2 relative BA** (w/Drug Interaction analysis component in 1 study), **3 Bioequivalence** (w/Food Effect component in 1 study), and **1 PK/PD study** (but no correlations made)

Filability and QBR comments

	"X" IF YES	COMMENTS
Application filable ?	X	**Need dissolution data for intermediate strengths (25/12.5 mg and 50/12.5 mg) since asking for biowaiver.**
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-956, HFD-110 (FrommE), HFD-860 (MehtaM, MarroumP, VelazquezL), CDR Central Document Room

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

/s/

Lydia Velazquez
8/14/2006 12:01:35 PM
BIOPHARMACEUTICS

Patrick Marroum
8/14/2006 03:49:41 PM
BIOPHARMACEUTICS

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