CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-956

PHARMACOLOGY REVIEW

NDA 21-956

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

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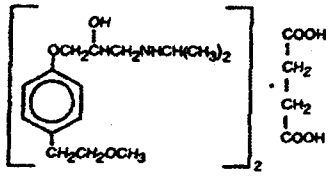
July 3, 2006

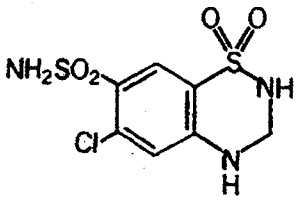
ORIGINAL NDA DATED: October 28, 2005
CENTER RECEIPT DATE: October 28, 2005
REVIEWER RECEIPT DATE: November 2, 2005

SPONSOR: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

DRUG: Trade name - ———
Generic name – metoprolol succinate extended release/hydrochlorothiazide



Metoprolol succinate (M.W. 652.8)



Hydrochlorothiazide (M.W. 297.74)

FORMULATION: ——— tablets (25/12.5, 50/12.5 or 100/12.5 mg) are formulated to contain 23.75, 47.5 or 95 mg metoprolol succinate extended release (equivalent to 25, 50 or 100 mg of metoprolol tartrate, respectively) and 12.5 mg of hydrochlorothiazide (HCT). Inactive ingredients include silicon dioxide, ethylcellulose, hydroxypropyl cellulose, corn starch, microcrystalline cellulose, polyvinyl pyrrolidone, sodium stearyl fumarate, hydroxypropyl methylcellulose, polyethylene glycol 6000, titanium dioxide, iron oxides yellow and red, ——— and ——— paraffin. ——— and ——— are used as solvents.

PHARMACOLOGICAL CLASS: Metoprolol succinate – $beta_1$-selective adrenoceptor blocking agent; Hydrochlorothiazide – diuretic and antihypertensive

PROPOSED INDICATION: Treatment of hypertension

PROPOSED DOSAGE REGIMEN: Proposed labeling recommends that dosing be individualized based on experience with the individual agents. Available tablet strengths permit starting at doses as low as 25/12.5 or 50/6.25 mg/day with subsequent titration every 2 weeks up to a maximum of 200 mg metoprolol and 25 mg HCT once daily.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: IND 67,095

RELATED NDAs: Toprol-XL (metoprolol succinate, NDA 19962), Lopressor HCT (metoprolol tartrate/hydrochlorothiazide, NDA 18303), Hydrodiuril (hydrochlorothiazide, NDA 11835), Ziac (bisoprolol fumarate/hydrochlorothiazide, NDA 20186)

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EXECUTIVE SUMMARY

Background

A combination product of metoprolol succinate extended release and hydrochlorothiazide has been developed for the treatment of hypertension. Metoprolol, a β1 selective antagonist, has been shown to lower blood pressure in hypertensive animals as well as in hypertensive patients. Animal and human studies have shown that metoprolol reduces sinus rate, slows the conduction in the atria and AV node and decreases cardiac contractility with a resultant decrease in cardiac output. Metoprolol also suppresses renin activity, thereby decreasing arterial pressure. Metoprolol succinate (Toprol-XL®) is approved in the U.S. for the treatment of hypertension, either alone or in combination with other antihypertensive agents.

Hydrochlorothiazide (HCT) is a marketed diuretic agent used for the treatment of hypertension. It inhibits the distal renal tubular electrolyte reabsorption, thereby increasing natriuresis. Several clinical studies have clearly confirmed the blood pressure lowering effect of HCT when used alone or in combination with other antihyper-tensive agents.

A combination of immediate-release metoprolol tartrate with HCT (Lopressor HCT®) is currently approved in the U.S. for the treatment of hypertension. An extended-release succinate salt of metoprolol with HCT has been marketed in Europe since 1989, and has been approved since then in more than ten countries.

I. Recommendations

A. Recommendation on Approvability

The combination product of extended release metoprolol succinate and hydrochlorothiazide is approvable from a nonclinical perspective.

B. Recommendations for Nonclinical Studies

None

C. Recommendations on Labeling

1. Sponsor's proposed text under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** presently reads as follows:

1 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

We recommend that the text under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** *be revised to read as follows:*

Metoprolol and Hydrochlorothiazide
Carcinogenicity and mutagenicity studies have not been conducted with the combination of metoprolol succinate or tartrate and hydrochlorothiazide.

The combination of metoprolol tartrate and hydrochlorothiazide produced no adverse effects on fertility or reproductive performance in rats at doses up to 200/50 mg/kg/day [about 10 and 20 times the maximum recommended human dose (MRHD) for metoprolol and hydrochlorothiazide, respectively, on a mg/m^2 basis].

Metoprolol
Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at oral dosage levels of up to 800 mg/kg/day (about 39 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at oral dosage levels of up to 750 mg/kg/day (about 18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility was observed in a study in which metoprolol tartrate was administered to male and female rats at doses up to 500 mg/kg/day, about 25 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60 kg patient.

Hydrochlorothiazide
Two-year feeding studies in mice and rats, uncovered no evidence of carcinogenic potential of hydrochlorothiazide in female mice at doses of up to 600 mg/kg/day (about 120 times the MRHD of 25 mg/day), or in male and female rats at doses of up to 100 mg/kg/day (about 40 times the MRHD). However, there was equivocal evidence of hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in the Ames test and the *in vitro* Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test and in the mouse Lymphoma Cell (mutagenicity) assay.
Aspergillus nidulans nondisjunction assay,

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4

mg/kg/day (about 20 and 1.6 times the MRHD, on a mg/m^2 basis), respectively, prior to mating and throughout gestation.

2. Under **PRECAUTIONS, Pregnancy,** sponsor's proposed header and text presently read as follows:

We recommend that this section of the proposed labeling be revised to read as follows:

Pregnancy
Pregnancy Category C
Metoprolol and Hydrochlorothiazide
Oral administration of metoprolol tartrate/hydrochlorothiazide combinations to pregnant rats during organogenesis at doses up to 200/50 mg/kg/day (10 and 20 times the MRHD for metoprolol and hydrochlorothiazide, respectively) or to pregnant rabbits at doses up

to 25/6.25 mg/kg/day (about 2.5 and 5 times the MRHD for metoprolol and hydrochlorothiazide, respectively) produced no teratogenic effects. A 200/50 mg/kg/day metoprolol tartrate/hydrochlorothiazide combination administered to rats from mid-late gestation through lactation produced increased post-implantation loss and decreased neonatal survival.

There are no adequate and well-controlled studies in pregnant women. should be used during pregnancy only if clearly needed.

Metoprolol
Metoprolol tartrate increased post-implantation loss and decreased neonatal survival in rats at a dose of 500 mg/kg/day, about 25 times the daily dose of 200 mg in a 60-kg patient, on a mg/m^2 basis. Similar effects were not observed at 50 mg/kg/day.

Hydrochlorothiazide
Hydrochlorothiazide administered to pregnant mice and rats during organogenesis at doses up to 3000 and 1000 mg/kg/day (600 and 400 times the MRHD), respectively, produced no harm to the fetus. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

II. Summary of Nonclinical Findings

Nonclinical studies conducted with the succinate or tartrate salts of metoprolol were submitted and reviewed under NDA 19-962 (Toprol-XL®), and AstraZeneca refers to that NDA to support the current NDA for the combination product, metoprolol succinate/hydrochlorothiazide. The nonclinical data for hydrochlorothiazide are taken from the published literature. The nonclinical combination studies submitted in support of the current NDA were previously submitted to the FDA by the Ciba-Geigy Corporation in support of their combination product, Lopressor HCT® Tablets (NDA 18-303), currently marketed in the U.S. by the Novartis Pharmaceutical Corporation. These combination studies include single dose studies, six-month general toxicity studies in rats and dogs and reproductive toxicity studies in rats and rabbits. Metoprolol tartrate was used for these studies except for the single dose mouse and rat studies that used both the tartrate and succinate salts. Studies in dogs have shown that after oral administration of equimolar doses of metoprolol tartrate or succinate for 5 days, the steady state plasma levels for metoprolol are virtually identical for both salt forms (NDA 19-962).

A 4:1 combination of metoprolol tartrate and HCT was used for the six-month oral toxicity studies conducted in rats (0, 80/20, 160/40 or 320/80 mg metoprolol/HCT/kg/day) and dogs (0, 20/5, 40/10 or 80/20 mg metoprolol/HCT/kg/day). These studies did not reveal any significant treatment-related findings except for

significantly increased adrenal weights in high dose male and female rats. There were no macroscopic or microscopic findings in these studies.

In fertility and developmental toxicity studies in rats, oral administration of metoprolol/ HCT combinations at doses up to 200/50 mg/kg/day [about 10 and 20 times the maximum recommended human dose (MRHD) for metoprolol and HCT, respectively, on a mg/m^2 basis] produced no adverse effects on fertility or reproductive performance, or produced any harm to the fetus. In pregnant rabbits, metoprolol/HCT combinations at doses up to 25/6.25 mg/kg/day (about 2.5 and 5 times the MRHD for metoprolol and HCT, respectively) produced no teratogenic effects. In a peri – and post – natal development study in rats, a 200/50 mg/kg/day metoprolol/HCT combination administered from day 15 of gestation through lactation produced increased post-implantation loss and decreased neonatal survival. It is noted that the above findings were also observed when metoprolol tartrate was given alone.

The above animal studies did not reveal any adverse effects of the combination product that would not have been expected of the individual components.

There are no approvability issues for the metoprolol succinate extended release/HCT combination product from the nonclinical toxicity testing program persective.

Reviewer Signature: _____

Supervisor Signature: Concurrence _____
Charles A. Resnick, Ph.D.

PHARMACOLOY/TOXICOLOGY REVIEW

[The pharmacology, pharmacokinetics and toxicology studies conducted with the succinate or tartrate salts of metoprolol were submitted and reviewed under NDA 19-962, and AstraZeneca refers to that NDA to support the current NDA for the combination product, metoprolol succinate/hydrochlorothiazide. The nonclinical data for hydrochlorothiazide (HCT) are taken from the published literature. The toxicology studies on the combination (conducted with 4:1 combinations of metoprolol and HCT) include single dose studies in mice and rats, six-month studies in rats and dogs, and reproductive toxicity studies in rats and rabbits. Metoprolol tartrate was used for these combination studies except for the single dose mouse and rat studies that used both tartrate and succinate salts. (Studies in dogs have shown that after repeated oral administration of equimolar doses of metoprolol tartrate or succinate for 5 days, the steady-state plasma levels for metoprolol are virtually identical for both salt forms.)

The nonclinical combination studies submitted in support of the current NDA, were previously submitted to the FDA by the Ciba-Geigy Corporation in support of their combination product, Lopressor HCT Tablets (NDA 18-303). These studies were reviewed by Dr. Charles A. Resnick (Review and Evaluation of Preclinical Data dated 6/11/1979). Summaries of the acute toxicity studies and Dr. Resnick's review of six-month toxicity studies and reproductive toxicity studies are provided below.]

Acute Toxicity Studies

Acute toxicity studies were conducted in mice and rats by the AB Astra Safety Assessment Laboratory, Sweden, using a mixture of metoprolol succinate and HCT (4:1 ratio).

Groups of NMRI mice (5/sex/group) were given single oral doses of the mixture at 400, 800 or 1600 mg/kg. The animals were observed for clinical signs/mortality for 14 days. There were no clinical signs at the low dose. At 800 mg/kg, reduced spontaneous movement and reduced frequency of respiration were noted up to 5 hours post-dose. No deaths occurred at this dose level. At 1600 mg/kg, most animals showed convulsions followed by death within 10 to 15 min post-dose. Seven of 10 animals died on day 1. One animal survived; of the remaining two, one died 30 hours post-dose and the other died on day 5. The LD_{50} was estimated to lie between 800 and 1600 mg mixture/kg.

A similar acute toxicity study was conducted in rats. Groups of Sprague-Dawley rats (5/sex/ group) were given single oral doses of the drug mixture at 1250, 2500 or 5000 mg/kg and the animals were observed for 14 days. All animals at 5000 mg/kg, 8 of 10 animals at 2500 mg/kg and 1 of 10 at 1250 mg/kg died on day 1. Clinical signs included ataxia, twitching, tremor, prostration and cyanosis followed by death. The LD_{50} was estimated to lie between 1250 and 2500 mg mixture/kg.

In acute toxicity studies conducted (by Astra Pharmaceuticals, Sweden) with a mixture of metoprolol *tartrate* and HCT (4:1 ratio), the oral LD_{50} values were found to be 5600 mg mixture/kg for male rats and 1800 mg mixture/kg for male mice.

Repeat-dose Toxicity Studies

SIX MONTH ORAL TOXICITY STUDY IN DOGS:

(——— Project No. 75-1201; histopath. evaluation by ——

Strain and Age of Animals: Beagle ———) 6-7 months of age.

Drug Administration:

Metoprolol/hydrochlorothiazide as combination tablets administered twice daily (at least four hours apart) as 4:1 ratio.

20 mg/kg/day metop./5 mg/kg/day hydro.	(5 males, 5 females)
40 mg/kg/day metop./10 mg/kg/day hydro.	(5 males, 5 females)
80 mg/kg/day metop./20 mg/kg/day hydro.	(5 males, 5 females)
Control group received placebo tablets	(5 males, 5 females)

Observations:

All animals observed daily for physical appearance, signs of local or systemic toxicity, pharmacologic effects or mortality. Physical examinations performed pretest and weekly, ophthalmoscopic examinations performed pretest and terminally. Body weights determined pretest and weekly, food consumption (estimated) four times weekly beginning pretest. EKGs obtained pretest and week 4, 12 and 26 (one hour after dosing). Hematologies, clinical chemistries and urinalyses carried out pretest, 1, 3 and 6 months. Post mortems included determination of weights of liver, spleen, kidney, heart, adrenal, thyroid and gonads. Full histopathological examination carried out.

Mortality: None

Drug Associated Findings:

A slight but consistent decrease in weight gain (relative to control) was noted in females receiving 80/20 mg/kg/day. Slightly lower food consumption was observed for both this as well as the 40/10 female group. Nonspecific EKG changes (ST depression at mid and high dosage at all examinations; T-wave changes at all dose levels at six months) were not attributed to drug administration. Mean potassium values of all compound treated male and female groups were lower than control at all intervals. A slight, non-dose related elevation in SGPT was observed in all treated female groups at six months. Lower mean

globulin values were noted in high dose males at all intervals. Report notes, however, that this value was also slightly lower than control pretest and that there were no compound related differences in the mean albumin and A/G ratio. Higher absolute and relative weights were reported at autopsy for thyroids of males and females of all treated groups, for kidneys of males and females of the high dose group, for spleens of males of all treated groups, for testicles of males of mid and high dose groups and for hearts of females of the high dose group. There was no microscopic or macroscopic evidence of tissue change associated with treatment.

SIX MONTH ORAL TOXICITY STUDY IN RATS:

[redacted] Project No. 75-1200; histopath. evaluation by [redacted]

Strain and Age of Animals:

Sprague Dawley (Charles River)of unstated age (mean weight prior to initial treatment 228 g for males, 141 g for females).

Drug Administration:

Metoprolol/hydrochlorothiazide as 4:1 combination suspension in 0.5% methocel, administered by intubation once daily:

80 mg/kg/day metop./20 mg/kg/day hydro.	(25 males/25 females)
160 mg/kg/day metop./40 mg/kg/day hydro.	(25 males/25 females)
320 mg/kg/day metop./80 mg/kg/day hydro.	(25 males/25 females)
Control group received methocel.	(25 males/25 females)

Observations:

All animals observed twice daily for mortality and gross signs of toxicologic or pharmacologic effect, detailed physical examination (including palpation for tissue masses) performed weekly. Ocular and otic examinations and determination of water consumption performed pretest, week one and monthly thereafter. Body weights determined pretest and weekly, food consumption weekly. Hematology, clinical chemistry and urinalysis studies performed on ten rats/sex from control and high dosage groups after 1, 3 and 6 months (mid and low dose animals examined only if indicated by findings at high dose level). Post mortem included determination of weights of adrenals,

gonads, heart, pituitary, spleen, liver and kidneys. Full histopathological examination performed on 10 rats/sex from control and high dosage groups.

Mortality	Dying First 3 Weeks and Replaced*	Later Deaths Not Replaced
Control:	1F (day 19)	2F (days 35&158)
Low Dose:	1M, 1F (day 18)	4M (days 43-144) 4F (days 22-46)
Mid Dose:	3M (day 18)	5M (days 42-133) 2F (days 38&28)
High Dose:	2M (day 2&6) 1F (day 18)	4M (days 21-155) 3F (days 61-17)

*Replacements not carried for full six months; the animals replaced were apparently not autopsied. All but one (mid dose) of male deaths during first 3 weeks attributed to faulty intubation. Cause of any other death in this study not specified. Scheduled sacrifices in this study carried out between days 186 and 189.

Drug Associated Findings:

As seen above, the increased mortality incidence associated with drug administration was not dosage dependent and the report states that gross autopsy findings were not indicative of a compound related effect. Slightly low (relative to concurrent control) hemoglobin, hematocrit and erythrocyte values of treated groups, at some intervals, were not dosage related and did not progress with time. Slightly high (relative to control) alkaline phosphatase values in males, at all intervals, did not represent a statistically significant finding at 6 months. Absolute and relative mean adrenal weights of high dose males and females and mid dose females were significantly higher than control adrenal weights. Histopathological examination revealed no effects in any of tissues examined which were attributable to compound administration.

SEGMENT I REPRODUCTION STUDY IN RATS:

(Astra Pharmaceuticals, Sweden; Project No. 752, Study No. 77052)

Mixture of metoprolol tartrate and hydrochlorothiazide was administered (in methocel suspension) at a constant ratio of 4:1 at total (metop. + hydro.) dose levels of 12.5, 62.5 or 250 mg/kg/day to groups of sexually

mature male and female SPF Sprague-Dawley rats. There were 15 males and 30 females in each of these groups as well as in a fifth group which served as vehicle control. Males were dosed from nine weeks prior to mating through the end of the mating period. Dosing of females began two weeks prior to mating, continuing up to 21 days post partum.

Half of the females were sacrificed on day 14 of pregnancy and examined with respect to number of corpora lutea, implantations, dead and live fetuses with gross examination of abdominal and thoracic cavities performed. Remaining females allowed to litter normally with litters examined at delivery for size, number stillborn and live fetuses and presence of gross abnormalities. All of these litters inspected daily for dead and abnormal young and litter weights and numbers of pups/litter recorded at delivery and again on days 7 and 21 post partum. On day 21 post partum all pups were sacrificed and examined externally and internally for abnormalities. Effects on parent animals studied by recording clinical signs, body weights, food consumption, estrus cycles, mating performance, conception rate and pre and post implantation losses. Attention also paid to length of gestation period, the process of parturition and to nursing and lactation. On day 21 post partum dams were sacrificed and a limited macroscopic examination of thoracic and abdominal cavities performed.

There were 25-28 confirmed pregnancies in each group (11-15/group which were sacrificed on day 14, 11-15/group which were allowed to litter). Distribution of these values did not indicate any effect of drug. There were no deaths and no signs of dysfunction observed in any of parent animals which were attributed to drug. Two deaths were attributed to intubation errors, one in a control at parturition (with 15 fetuses) and one in a high dose dam at day 0 of gestation. Adverse effects on litters limited to a significant decrease in mean pup mass at birth for all treated vs control group pups. Only the high dose group continued to show this apparent effect at 7 and 21 days post partum. Report notes that litter mass was not decreased.

SEGMENT II REPRODUCTION STUDY IN RATS:

(Astra Pharmaceuticals, Sweden; Project No. 752, Study No. 77009)

Daily doses of 10.0/2.5, 50/12.5 and 200/50 mg/kg metoprolol tartrate/

hydrochlorothiazide administered orally from day 6 to day 15 of pregnancy to groups of 20 inseminated Sprague-Dawley rats. A fourth group served as vehicle control (1.5% Methocel). We note that four dams of each of control, mid and high dosage groups and two dams of the low dose group, did not become pregnant. An additional two control dams and one low dosage dam suffered total litter loss.

Effects on dams were studied by recording clinical signs, body weights and food consumption. On day 21 of pregnancy dams were sacrificed and uterine contents examined with respect to implantations, viable and dead young, resorption sites and litter and pup weights. All pups examined externally. Every third litter sectioned for visceral anomalies. Remaining litters cleared and stained with alizarin for skeletal anomalies.

There were no deaths or signs of dysfunction in any of dams. There was a slight retardation of body weight gain in the high dose dams but only during first three days of dosing. Types and frequencies of abnormalities were comparable in all groups.

SEGMENT II REPRODUCTION STUDY IN RABBITS

(Astra Pharmaceuticals, Sweden; Project No. 752, Study No. 77009)

Daily doses of 5.0/1.25, 12.50/3.13 and 25.00/6.25 mg/kg metoprolol tartrate/hydrochlorothiazide administered orally during days 6-18 of gestation to groups of 13 or 14 inseminated New Zealand White rabbits. A fourth group served as vehicle control (1.5% methocel).

Effects on dams were studied by recording clinical signs, body weights and food consumption. On day 29 of pregnancy dams were sacrificed and uterine contents examined with respect to implantations, viable and dead young, resorption sites and weights of viable young. Ovaries examined with respect to number of corpora lutea. All pups were examined externally for abnormalities. Skeletons then cleared and stained with alizarin to detect skeletal abnormalities.

There were two maternal deaths (due to intubation error) in control and low dosage groups during the 2nd week of gestation. After subtracting those deaths along with non-pregnant dams (one control, two mid dose and one high dose) one (high dose) dam with total litter loss and one (low dose) dam excluded because of a dosing omission, there

were 11-12 dams with viable young remaining. Litter size was slightly decreased and fetal loss and weight increased at the highest dosage. Differences were not statistically significant. Types and incidences of abnormalities were comparable in all groups. Frequency of skeletal variants (extra rib and unossified sternebrae) was slightly, nonsignificantly elevated in all compound treated groups.

SEGMENT III REPRODUCTION STUDY IN RATS

(Astra Pharmaceuticals, Sweden; Project No. 752, Study No. 77065)

Daily dose of 10.0/2.5, 50/12.5 and 200/50 mg/kg methoprolol tartrate/hydrochlorothiazide administered orally from day 15 of gestation to day 21 post partum to groups of 20 inseminated Sprague-Dawley rats. A fourth group served as vehicle control (1.5% Methocel). Pregnancies could not be confirmed for six control, eight low, two mid and one high dose dam. Two additional controls and one additional high dose dam were excluded (reason unspecified) and two additional controls and one additional high dose dam suffered total litter loss. There remained 10, 12, 18 and 17 litters with viable young in control, low, mid, and high dose groups, respectively.

Effects on dams were studied by recording clinical signs, body weights and food consumption. Duration of gestation recorded with special attention paid to labor, delivery and lactation. At delivery litters examined for size, stillborns, live fetuses and presence of gross abnormalities. Litter size and weights of pups recorded at delivery and again on days 7 and 21 post partum. Time of occurrence of physical developmental milestones such as pinna unfolding, tooth eruption, generalized hair growth and eye opening were recorded. On day 21 all pups were sacrificed and examined externally and internally for abnormalities. Dams also sacrificed at this time with limited macroscopic examination of thoracic and abdominal cavities performed.

There were no deaths or signs of dysfunction in any group. There was a slight retardation of body weight gain in high dose dams during the first three days of dosing. Litter size at birth was slightly reduced relative to control at this dosage as was mean pup weight (slight but not significant reduction in mean pup weight day 7 and day 21). Cumulative (fetal and pup) loss at 21 days was statistically elevated at the highest dosage level when compared with loss at birth but not when compared with loss of control group at 21 days.

OVERALL SUMMARY AND EVALUATION

A combination product of extended release metoprolol succinate and hydrochlorothiazide (HCT) has been developed for the treatment of hypertension.

Metoprolol is a β_1- selective (cardioselective) adrenergic receptor-blocking agent with no intrinsic sympathomimetic activity. Animal and human studies have shown that metoprolol slows the sinus rate, decreases the spontaneous rate of depolarization of ectopic pacemakers, slows the conduction in the atria and AV node and decreases cardiac contractility. The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. Some of the suggested possible mechanisms include: (1) competitive antagonism of catecholamines at peripheral 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. Metoprolol succinate (Toprol-XL®) has been approved in the U.S. for the treatment of hypertension, either alone or in combination with other antihypertensive agents, long-term treatment of angina pectoris, and for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive or cardiomyopathic origin. For hypertension, a starting daily dose of 50 to 100 mg is recommended, with dose increases up to 400 mg once daily.

HCT is a marketed diuretic agent used for the treatment of hypertension and edema associated with congestive heart failure, hepatic cirrhosis, nephritic syndrome, chronic renal failure and acute glomerulonephritis. It inhibits distal renal tubular electrolyte reabsorption, thereby increasing the excretion of sodium and chloride. Natriuresis is accompanied by some potassium and bicarbonate loss. Although the antihypertensive mechanism of HCT is not well established, clinical trials have clearly confirmed the blood pressure lowering effect of HCT when used alone or in combination with other drugs. The recommended daily dose for HCT is 25 to 50 mg, although lower doses (12.5 or 6.25 mg) have also been shown to lower BP if combined with other agents. Combined administration of HCT with other antihypertensive agents such as beta-blockers, ACE inhibitors and angiotensin receptor blockers has been shown to produce antihypertensive effects that are generally additive.

A combination of an immediate-release formulation of metoprolol tartrate with HCT (Lopressor HCT®) is currently approved for the treatment of hypertension.

Proposed labeling recommends that dosing with the metoprolol succinate extended release/HCT combination product be individualized based on experience with the individual agents. Available tablet strengths permit starting at doses as low as 25/12.5 or 50/6.25 mg/day with subsequent dose titration every 2 weeks up to a maximum of 200/25 mg once daily.

Studies in dogs have shown that after repeated oral administration of equimolar doses of metoprolol tartrate or succinate, the steady-state plasma levels for metoprolol are virtually identical for both salt forms.

The nonclinical studies conducted with the 4:1 combination of metoprolol and HCT and submitted in support of the current NDA are summarized below.

Acute oral toxicity studies in rats and mice conducted with the mixture of metoprolol succinate and HCT showed that the LD_{50} values lie between 1250 and 2500 mg mixture/kg for male and female rats, and between 800 and 1600 mg mixture/kg for male and female mice. For the mixture of metoprolol tartrate and HCT, the oral LD_{50} values were found to be 5600 mg mixture/kg for male rats and 1800 mg mixture/kg for male mice.

In a six-month oral toxicity study, metoprolol tartrate/HCT was administered to Sprague-Dawley rats (25/sex/group) by oral intubation at dose levels of 0, 80/20, 160/40 and 320/80 mg/kg/day. There were no significant treatment-related findings except for adrenal weights in high dose males and females (both absolute and relative to body weight) that were elevated above concurrent control weights ($p \leq 0.01$). There were no treatment-related macroscopic or microscopic findings.

In another six-month toxicity study, metoprolol tartrate/HCT combinations were administered twice daily (at least four hours apart) to dogs (5/sex/group) in tablet form at dose levels of 20/5, 40/10 and 80/20 mg/kg/day. Electrocardiographic examination revealed increased incidences of ST depression (AVF lead) and tall peaked or large T waves in some dogs at all dose levels. According to Dr. [redacted] V.M.D, a canine cardiology expert, the above findings "remained within normal limits, and these non-specific changes can not be taken as evidence of untoward myocardial drug effect". It is noted that these effects were not dose-related; however, no NOAEL for the EKG finding was observed. Significantly lower than control serum potassium levels were noted in all treated male and female groups (not dose-dependent). Dose-related increased absolute and relative spleen weights were seen in all treated male groups (statistically significant only at the high dose). Increased heart weight was noted in high dose females. There were no treatment-related macroscopic or microscopic findings.

In a fertility and reproductive performance study, metoprolol tartrate/HCT combinations (0, 10/2.5, 50/12.5 or 200/50 mg/kg/day) were administered orally to male (from 9 weeks prior to mating and through the end of the mating period) and female (2 weeks prior to mating, continuing through mating, gestation and up to 21 days post partum) rats. There were no treatment-related adverse effects on fertility and reproductive performance in this study in which the highest dose was about 10 times the maximum recommended human dose (MRHD) of 200 mg metoprolol/day and about 20 times the MRHD of 25 mg HCT/day, on a mg/m^2 basis.

In a developmental toxicity study in rats, oral administration of metoprolol tartrate/HCT combinations (0, 10/2.5, 50/12.5 or 200/50 mg/kg/day) during organogenesis did not reveal any teratogenic effect of the test combination.

In rabbits, oral administration of metoprolol tartrate/HCT combinations (0, 5/1.25, 12.5/3.13 or 25/6.25 mg/kg/day) during organogenesis produced no adverse effects on

either fetus or dam. The highest dose in this study was 2.5 and 5 times the MRHD for metoprolol and HCT, respectively.

In a peri – and post – natal development study in rats, metoprolol tartrate/HCT combinations (0, 10/2.5, 50/12.5 or 200/50) were administered orally from day 15 of gestation to day 21 post partum. At the highest dose level (about 10 and 20 times the MRHD for metoprolol and HCT, respectively), the cumulative fetal and pup loss on day 21 was significantly increased compared to the loss at birth. However, overall loss was similar in the concurrent control group.

The above animal studies did not reveal any adverse effects of the combination product that would not have been expected of the individual components.

Both Toprol-XL and hydrochlorothiazide are marketed drugs, and the combination product, under this NDA, is being developed at doses within their respective approved dose ranges. Fixed dose combination tablets of metoprolol tartrate (an immediate release formulation) with HCT have been available since 1978. An extended release succinate salt of metoprolol and HCT (100/12.5 mg) has been marketed in Europe since 1989, and has been approved since then in more than ten countries. A large volume of post-marketing clinical experience has been accumulated for this combination product. According to the sponsor, safety reports have revealed no unique adverse effects of the combination product.

In conclusion, there are no approvability issues for the metoprolol succinate extended release/HCT combination product from the non-clinical toxicity testing program perspective.

RECOMMENDATIONS

The NDA is approvable. See Executive Summary for recommended changes to the sponsor's proposed labeling.