

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 29, 2007

TO: Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Mary Ross Southworth PharmD, Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: metoprolol succinate (Toprol XL; NDA 19-962)
Pediatric Exclusivity Approval Date: 07/18/2006

RCM#: 2007-253

Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of metoprolol succinate in pediatric patients. Up to the "data lock" date of August 22, 2007, AERS contained 2501 cases for metoprolol succinate (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 1% of the total (25/2501).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, July 18, 2006 to August 22, 2007. We used an AERS data lock of August 22, 2007 to allow time for reports received up to July 18, 2007 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 468 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.6% of the total number of cases (3/468).

There were 3 cases identified in AERS for review during the designated 1-year post-pediatric exclusivity period - all 3 cases were from foreign sources. The events in these cases were accidental ingestion, anemia, and drug exposure during pregnancy. In each of

these cases, it was not possible to make an association between the event and metoprolol succinate use due to the presence of complicating factors or lack of information.

One case (foreign) with an outcome of death was also identified (from outside of the 1-year post-pediatric exclusivity period). This case described fetal anomalies and death in the child of a mother who was on multiple medications for the treatment of hypertension and who did not appear to receive prenatal care until the 27th week of pregnancy.

In conclusion, this review did not identify any serious unexpected events associated with metoprolol succinate use in pediatric patients. We will continue to monitor reports of adverse events associated with metoprolol succinate.

1.0 Background

Metoprolol succinate, a beta adrenergic blocker (marketed as TOPROL-XL by AstraZeneca), was approved by the FDA on January 10, 1992. It is approved for the following indications: hypertension, angina pectoris, and heart failure. The Agency approved a supplemental NDA which added information to the label regarding its use in pediatric hypertensive patients ≥ 6 years of age on July 18, 2007 (see section 2.3). However, it was determined that the data submitted in the NDA were insufficient to recommend a new indication for pediatric use of metoprolol succinate, as the primary endpoint was not achieved (dose response for reduction in systolic blood pressure). Adverse reactions noted in the medical review¹ of the supplement included headache, URI, and bradycardia; no unusual events were noted.

A recent OSE safety review of metoprolol succinate² addressed two issues, a drug interaction with digoxin and the occurrence of cardiogenic shock in patients experiencing an acute MI who received metoprolol succinate. Both of these events were added to the label of metoprolol succinate (in the PRECAUTIONS/ Drug Interactions section and Post-Marketing Experience sections, respectively).

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of metoprolol succinate in pediatric patients. Up to the "data lock" date of August 22, 2007, AERS contained 2501 cases for metoprolol succinate (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 1% of the total (25/2501).

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¹ Karkowsky A. Clinical Review of metoprolol succinate in pediatrics. 10/29/2006.

² Southworth MR. OSE review January 5, 2007, RCM #2006-736

of the total number of cases (3/468). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Toprol-XL Products

Toprol-XL (metoprolol succinate), NDA 19-962, which is sponsored by Astra Zeneca and approved in the US on January 10, 1992, is formulated in

Tablets: 25 mg, 50 mg, 100 mg, 200 mg

2.2 Toprol–XL approved indications

Toprol-XL is indicated for the treatment of hypertension, angina pectoris, and heart failure.

2.3 Toprol-XL Pediatric labeling

Pertinent pediatric labeling:

CLINICAL PHARMACOLOGY, Pharmacokinetics

Pediatrics

The pharmacokinetic profile of TOPROL-XL was studied in 120 pediatric hypertensive patients (6 to 17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol were similar to those described previously in adults. Age, gender, race, and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight, Metoprolol pharmacokinetics have not been investigated in patients <6 years of age.

PRECAUTIONS

Pediatric Use

One hundred forty-four hypertensive pediatric patients aged 6 to 16 years were randomized to placebo or to one of three dose levels of TOPROL-XL (0.2, 1.0, or 2.0 mg/kg once daily) and followed for 4 weeks. The study did not meet its primary end point (dose response for reduction in SBP). Some prespecified secondary end points demonstrated effectiveness including

- *Dose-response for reduction in DBP*
- *1.0 mg/kg vs. placebo for change in SBP, and*
- *2.0 mg/kg vs. placebo for change in SBP and DBP*

The mean placebo corrected reductions in SBP ranged from 3 to 6 mmHg, and DBP from 1 to 5 mmHg. Mean reduction in heart rate ranged from 5 to 7 bpm but considerably greater reductions were seen in some individuals. (See DOSAGE and ADMINISTRATION Pediatric Hypertensive Patients ≥ 6 years of age).

No clinically relevant differences in the adverse event profile were observed for pediatric patient aged 6 to 16 years as compared with adult patients.

Safety and effectiveness of TOPROL-XL have not been established in patients < 6 years of age.

DOSAGE AND ADMINISTRATION, Hypertension, Pediatric Hypertensive Patient ≥ 6 Years of age

If selected for treatment, the recommended starting dose of TOPROL-XL is 1.0 mg/kg once daily however, the maximum initial dose should not exceed 50 mg once daily. The minimum available dose is one half of the 25 mg TOPROL-XL tablet. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients

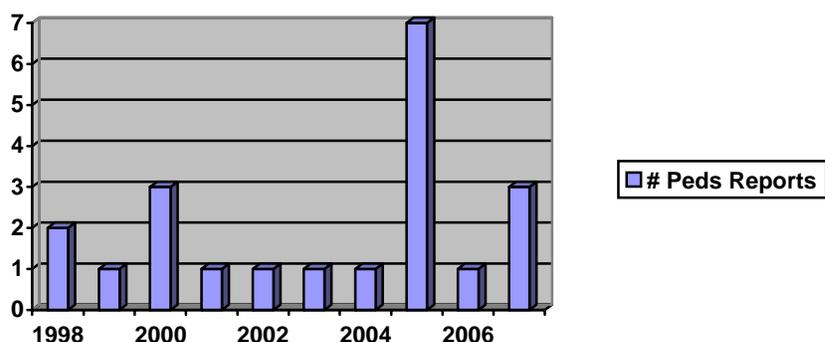
3. AERS Search Results: Metoprolol Succinate (TOPROL-XL)

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts ¹ of AERS Reports for All Sources from Marketing Approval Date (1/10/92 - 8/22/07) (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1917 (1436)	1438 (979)	145 (100)
Pediatrics (0-16 yrs.)	21 (12)	20 (11)	3 ³ (2)
Age unknown (Null values)	563 (522)	303 (265)	11 (7)
Total	2501 (1970)	1761 (1255)	159 (109)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.
³ Includes two miscoded death cases in a 27 year old and 69 year old (both US cases)

Figure 1: Reporting trend for pediatric reports from approval date (1/10/92) to 8/22/07:



3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts ¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (07/27/06-08/22/07) (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	386 (291)	355 (308)	47 (38)
Pediatrics (0-16 yrs) ³	4 (1)	4 (1)	1 (1)
Age unknown (Null Values)	78 (65)	61 (48)	1 (1)
Total	468 (357)	420 (357)	49 (40)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.
³ Includes one miscoded US case involving a 27 year old (death case)

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

Three pediatric cases were identified. In the first case (Brazil), a 2 year old female accidentally took 100 mg of metoprolol succinate and received activated charcoal. The patient was reportedly asymptomatic. No other information is available. In the second case (Brazil), a neonate (born at 34 weeks) was found to have a “moderate heart murmur”, bradycardia, and severe difficulty breathing. The mother had initiated metoprolol succinate 50 mg daily in her 5th month of pregnancy for the treatment of hypertension. No further information is available.

In the third case (Switzerland, case from the literature), a 12 year old male experienced severe anemia (“Hg 63 g/L”) 2 years following renal transplantation. His medical therapy consisted of mycophenolate mofetil, sirolimus, irbesartan, metoprolol, and amlodipine (duration of therapies unreported). He was treated with parenteral iron, erythropoietin, and irbesartan was withdrawn (the authors attributed the anemia to irbesartan) without improvement of his condition.

5 Pediatric Death Case

One pediatric death case was reported for metoprolol succinate during the entire marketing period (January 1992 to present). This case (Belgium, cited from the literature) describes a female neonate (born at 36 weeks) who was found to have limb deformities, pulmonary hypertension with PDA, abnormal kidney structure, and Potter's facies; she developed respiratory failure and died on day 4. The mother had been treated with metoprolol, felodipine, losartan, and hydrochlorothiazide for severe hypertension and became pregnant. She was "lost to follow up" until 27 weeks of gestation. Duration of therapies was unreported. No other information is available.

5. Summary/Recommendations

There were 3 cases identified in AERS for review during the designated 1-year post-pediatric exclusivity period, July 27, 2006 through August 22, 2007. Additionally, a second AERS search was conducted to identify death cases with metoprolol succinate since its approval (January 1992). This search identified one case. All 4 cases were reported from foreign sources.

Two of these cases involved *in utero* exposure to metoprolol succinate; in these cases, babies were born with various (potential) congenital abnormalities and/or fetal distress. In both cases, the mother was being treated for hypertension, which may be associated with increased fetal morbidity and mortality³. In one case multiple medications were taken by the mother in the prenatal period, including losartan, an angiotensin II antagonist, which has been associated with fetal renal anomalies when used during the second and third trimester. In addition, it appeared that there was a lack of prenatal care up to the 27th week of pregnancy in this case. In the second maternal case, metoprolol succinate was reported as monotherapy. However, the case lacked enough information to fully assess any contribution metoprolol use had on the event.

In the case of the 12 year old who developed anemia, multiple complicating factors could have contributed to his condition including kidney disease, and concomitant use of other medications associated with anemia (mycophenolate, sirolimus, irbesartan).

In conclusion, this review did not identify any serious unexpected events associated with metoprolol succinate use in pediatric patients. We will continue to monitor reports of adverse events associated with metoprolol succinate in pediatric patients.

Mary Ross Southworth, PharmD

concur:

Cindy Kortepeter, PharmD 8/29/07
Safety Evaluator Team Leader

³ Ferrer RL, et al. Management of mild chronic hypertension during pregnancy: A review. *Obstetrics and Gynecology* 2000; 96: 849-60.

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/s/

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9/27/2007 07:42:38 AM
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10/3/2007 10:27:43 AM
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