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(FORM UPDATED: 08/11/2010)

# WISCONSIN STATE LEGISLATURE ...
# PUBLIC HEARING - COMMITTEE RECORDS

## 2009-10
(session year)

## Senate
(Assembly, Senate or Joint)

## Committee on ... Health, Health Insurance, Privacy, Property Tax Relief, and Revenue (SC-HHIPPTRR)

## COMMITTEE NOTICES ...

- Committee Reports ... **CR**
- Executive Sessions ... **ES**
- Public Hearings ... **PH**

## INFORMATION COLLECTED BY COMMITTEE FOR AND AGAINST PROPOSAL

- Appointments ... **Appt** (w/Record of Comm. Proceedings)
- Clearinghouse Rules ... **CRule** (w/Record of Comm. Proceedings)
- Hearing Records ... bills and resolutions (w/Record of Comm. Proceedings)
  (**ab** = Assembly Bill) (**ar** = Assembly Resolution) (**ajr** = Assembly Joint Resolution)
  (**sb** = Senate Bill) (**sr** = Senate Resolution) (**sjr** = Senate Joint Resolution)
- Miscellaneous ... **Misc**

* Contents organized for archiving by: Stefanie Rose (LRB) (June 2012)

SB 354

# Generic Substitution of Anti-Epileptic Medications:

## A Clinical, Safety and Scientific Perspective

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State of Wisconsin
Assembly Public Health Committee
Senate Health, Health Insurance, Privacy, Property Tax Relief and Revenue
October 22, 2009

# Why am I here?

- Practicing physician
  - 22 years in clinical and academic practice
  - Board Certified in Internal Medicine and Cardiology
- Medical Director for Taro Pharmaceuticals
  - Oversee global Drug Safety
    - US, Canada, UK and Israel
  - Products include anti-epileptics
    - Carbamazepine, lamotrigine, levetiracetam, phenytoin
- Work with the Generic Pharmaceutical Association

# Clinical Perspective

- Our goal is to make sure that patients receive the safe and effective medications that they need
- This is true for all medical conditions, and especially true for patients with chronic, serious medical conditions such as epilepsy

# Treatments Must be Individualized

- The vast majority of patients with seizures will respond to a broad range of anti-epileptic medications
- Dosages should be monitored – but, most patients will achieve adequate control on a stable medical regimen with little variability in drug levels or therapeutic response

# Special Needs

- Occasionally patients with epilepsy have complex medical regimens and require particular attention to formulations and methods of administration
- Physicians already can specify the Reference Listed "Brand Name" product by indicating "***No substitution***"

# Accessibility Matters

- **No medication works unless it is taken**
- Patients with limited financial means often fail to fill prescriptions or miss doses because of the cost
- This is a recipe for disaster in patients with seizures
- Safe, effective and affordable medications are need for epilepsy patients

# Safe – Effective – Affordable

- What does the FDA do to establish bioequivalence?
- What is the safety track record of generic medications for patients with epilepsy?
- What prospective, scientifically valid information is available?

# FDA evaluates generics fully during the approval process

- The FDA evaluates the entire manufacturing process
  - Includes source of active pharmaceutical ingredient
  - All inactive ingredients meet USP standards
  - Manufacturing and testing controls are validated
  - Dissolution and stability testing must be the same as the brand
- FDA can mandate additional in process and release standards to make sure that the products are bioequivalent

# FDA can evaluate the full record in bioequivalence studies

- FDA has access to the full record for each individual patient in bioequivalence studies
- The FDA can identify outlier patients or site to site variability
- Bioequivalence required by FDA is more sophisticated than just the average pharmacokinetic response
  - It takes into account patient to patient variability
  - The response of individual patients must be similar in order to pass bioequivalence testing

# FDA Description of Bioequivalence Requirements

- **Steven K. Galson, M.D. – 2004**
  - Acting Director FDA Center for Drug Evaluation and Research
- "It *(the-20/--25% "rule")* actually represents acceptable bounds on the 90% confidence intervals around the ratio of the mean results for each of the two products. In practice, because of human variability, this means that the actual results for rate and extent have to be very close. FDA did a study in the 1980's evaluating 224 bioequivalence studies that "passed" the -20/+25 rule. In these studies, the average observed difference in absorption between the brand name and the generic was about 3.5%. It is important to note that FDA applies an identical bioequivalence standard to brand name products when significant changes in manufacturing or formulation occur. Nevertheless, the degree of regulatory control over rate and extent of absorption for any formulation is the same for a generic and branded drug."

# FDA monitors generic manufacturers just like the brands

- FDA routinely inspects generic manufacturing facility – must meet current Good Manufacturing Procedures
- Generic manufacturers submit annual reports on manufacturing processes and stability
- FDA is aware of manufacturing or stability issues
  - Branded companies may have the same or even more batch to batch variability than some generics
- *Only the FDA sees the full record for ALL manufacturers*

# FDA can best assess safety risks

- Both generic and branded manufacturers submit Adverse Event reports to the FDA
- FDA receives all the adverse event reports and can compare across various products

- *Only the FDA is in a position to know whether there is a safety issue related to a particular branded or generic formulation of a product*

# Example: Carbamazepine

- Long established anti-epileptic – brand name Tegretol®
- Generic versions have been available to patients for many years
- Generic medications are widely used
- Clinical studies support safety and efficacy of generic carbamazepine

# Generic Carbamazepine Long Track Record

- Generic Carbamazepine products have been on the market for >20 years
- They have been used by millions of epileptic patients
- Excellent safety record

| First Carbamazepine Approval | |
|---|---|
| Manufacturer | Year |
| Teva | 1986 |
| Actavis | 1987 |
| Taro | 1996 |
| Caraco | 2001 |
| Apotex | 2002 |
| Morton Grove | 2002 |

# Carbamazepine market

- Immediate release tablets, chewable tablets and suspension
  - Total US annual Rx's: 3.05 Million
  - Physicians cans choose Brand or Generic
- Extended release tablets and capsules
  - Total US annual Rx's: 1.88 Million
  - Available as brand products only

All Sales Data from Wolters Kluwer© - data through November 2007

# Generic Medications: Widely Accepted

- For all formulations for which generic products exist, the generic product outsells the branded products
  - Immediate release tablets
  - Chewable tablets
  - Suspension
- Brand name product from Novartis is not the market leader in any of these forms

# Carbamazepine formulations

200 mg Tablets

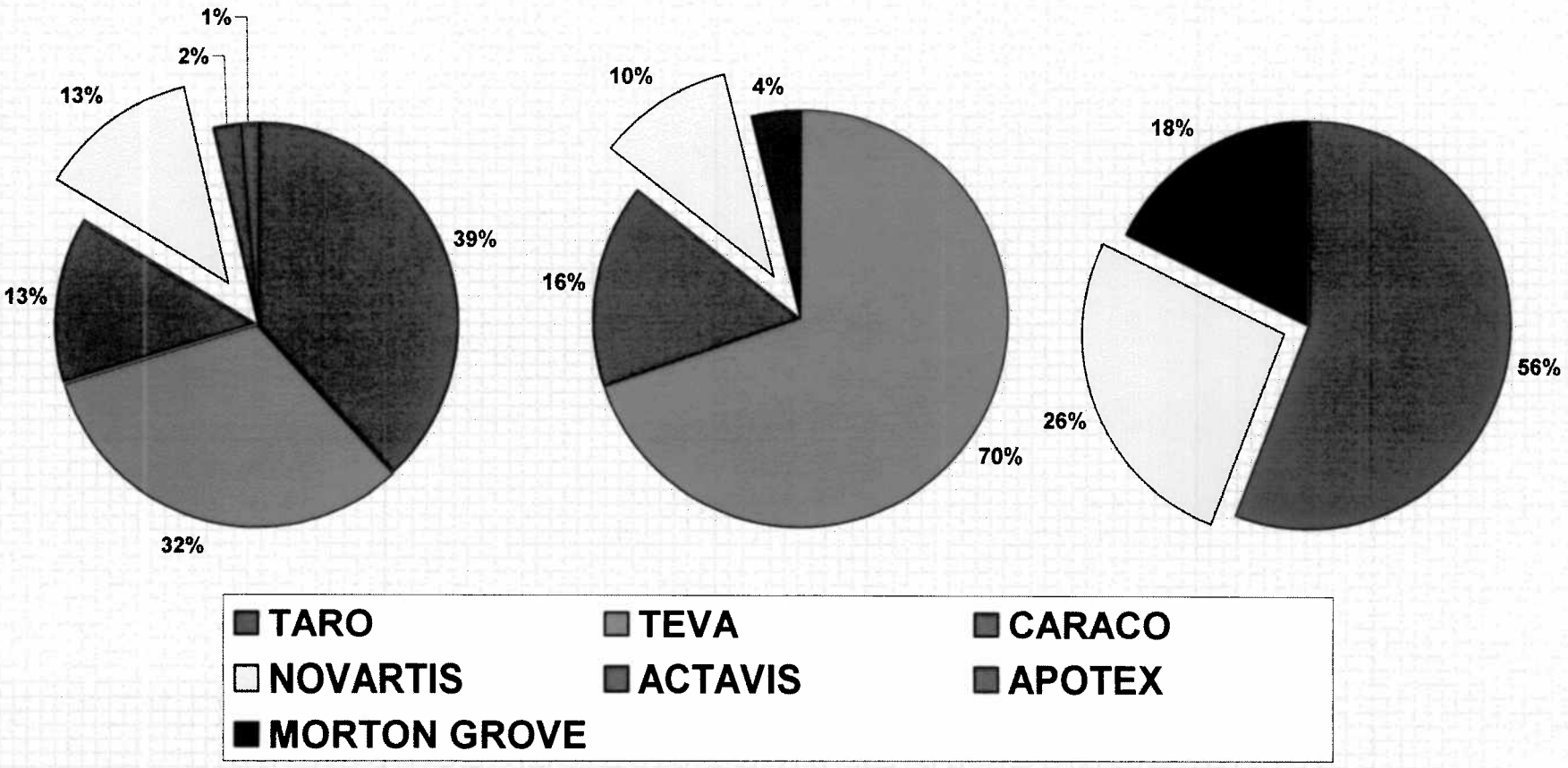
Rx = 2,430,000

100 mg Chewable

Rx = 483,000

100 mg/5mL Suspension

Rx = 133,000



# Published data on generic carbamazepine

- Prospective, randomized, controlled trials
- Multi-dose pharmacokinetic studies
- Clinical cross-over studies

# Multiple dose pharmacokinetics

## A multiple-dose safety and bioequivalence study of a narrow therapeutic index drug: A case for carbamazepine

**Avraham Yacobi, PhD, Steve Zlotnick, PharmD, RPh, John L. Colaizzi, PhD, Daniel Moros, MD, Eric Masson, PharmD, Zohreh Abolfathi, PhD, Marc LeBel, PharmD, Rakesh Mehta, PhD, Yechiel Golander, PhD, and Barric Levitt, MD**

*Hawthorne, New York, and Bronx, NY, East Brunswick, NJ, and Sainte-Foy, Quebec, Canada*

CLINICAL PHARMACOLOGY & THERAPEUTICS

APRIL 1999

Study conducted by Taro along with Rutgers University and Anapharm

# Study design

- Compared an FDA approved generic formulation to the branded product
- Subjects (n=28) received generic product for 7 days compared to branded product for 7 days

# Brand and Generic Products Are Very Similar

| | Generic | Brand |
|---|---|---|
| **% Average Tablet Content** | 101 | 98.6 |
| **Content Uniformity** | | |
| **% Average Tablet Content** | 100 | 100 |
| **% Lowest Assay Value** | 99.0 | 95.6 |
| **% Highest Assay Value** | 102 | 103 |
| **%RSD** | 1.1 | 2.2 |

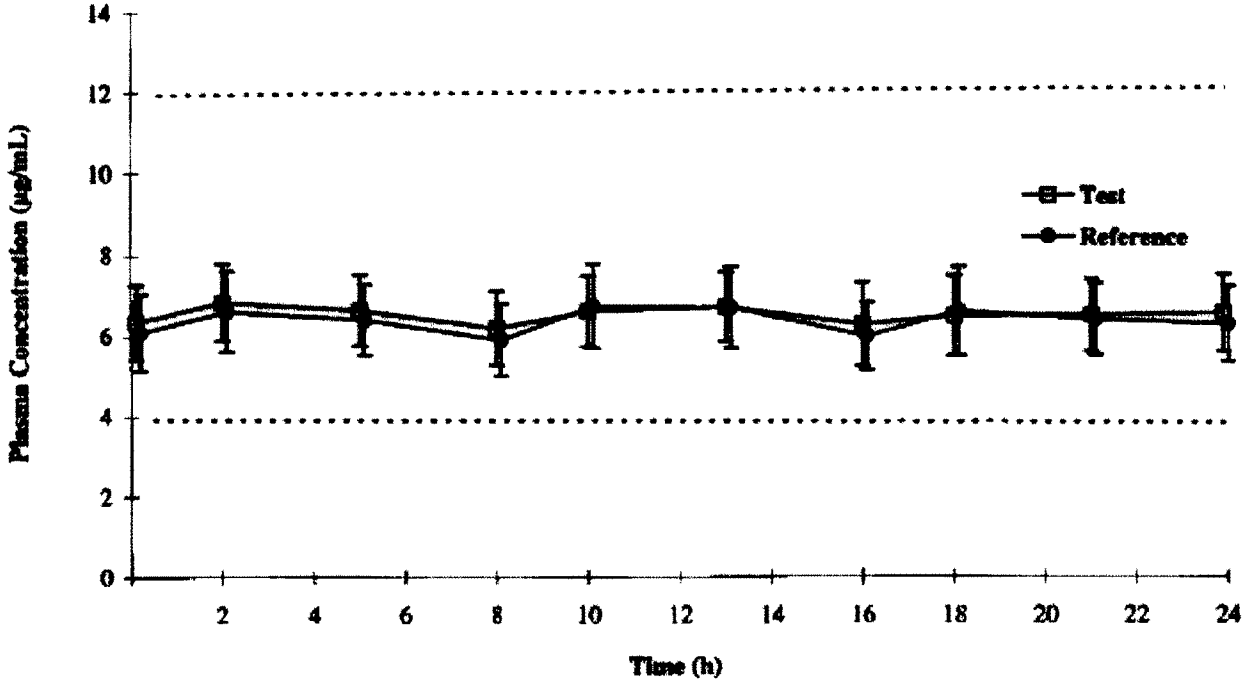
- Generic has slightly ***lower*** variability than Brand

# Steady State Cross-Over Results

| | Mean values (CV%) | | | | |
|---|---|---|---|---|---|
| Parameter | Generic | Brand | Ratio | p-Value | 90% CI |
| AUC (µg•h/mL) | 156 (13.2) | 153 (13.7) | 1.02 | NS | 100-104 |
| Cmax (µg/mL) | 7.11 (12.9) | 7.10 (12.9) | 1.0 | NS | 98-103 |
| Cmin (µg/mL) | 5.90 (15.1) | 5.65 (14.8) | 1.04 | T>R | 102-107 |
| Cavg (µg/mL) | 6.52 (13.2) | 6.39 (13.7) | 1.02 | NS | 100-104 |
| tmax (h) | 11.6 (76.3) | 12.6 (52.8) | 0.92 | NS | |
| Fluctuation % | 18.8 (31.8) | 23.0 (31.6) | 0.82 | T<R | |

- All metabolic parameters are within 4% of each other
- Fluctuation was slightly greater with Brand

# Steady State Profile




- Blood levels are very stable over time
- No difference between Brand and Generic

# Conclusions from multi-dose pharmacokinetic study

- No difference in metabolic parameters between Brand and Generic
- Levels of carbamazepine and its metabolite are very stable at steady state
  - Less than 5% variability
- FDA criteria of bioequivalence confirmed in multi-dose study

# US cross-over study in patients with epilepsy

- Randomized, double-blind, cross-over study in 40 epileptic patients taking carbamazepine for 6 or more months
  - 13 to 70 yeas-old
- Received 90-day courses of treatment with Brand and Generic
  - Order determined at random

Oles KS, Penry JK, Smith LD, Anderson RL, Dean JC, Riela AR. Therapeutic bioequivalency study of brand name versus generic carbamazepine.Neurology. 1992 Jun;42(6):1147-53.

# Clinical Patient Types

- Looked at a wide variety of patient types
- Included patients who were "well-controlled" on carbamazepine alone
- Also included patients who were on carbamazepine along with other medications and still having seizures

# Blood level results

- No difference in blood level concentrations between Brand and Generic
  - Difference < 5%
- No difference in Fluctuation Index over 3 month treatment period

# Conclusion from US cross-over study in patients with epilepsy

- Patient outcomes were the same on Brand and Generic
- No difference in overall seizure frequency between Brand and Generic
- No difference in breakthrough seizures in "controlled patients"
- Breakthrough seizures were NOT related to changes in blood level between products
- No difference in side-effects

# International Studies

- European Study compared Novartis Tegretol to 2 European generic products
- Found no difference in blood levels between the products
- All products equally well tolerated
- No difference in side effects

Aldenkamp AP, Rentmeester T, Hulsman J, Majoie M, Doelman J, Diepman L, Schellekens A, Franken M, Olling M. Pharmacokinetics and cognitive effects of carbamazepine formulations with different dissolution rates. Eur J Clin Pharmacol. 1998 Apr;54(2):185-92.

# International Studies

- Asian study compared Novartis Tegretol to 3 generic products
- 18 patients with epilepsy treated for 3 weeks with each product
  - Age range 15-49
  - Dose 400-1000 mg (average 677 mg/day)
  - Concomitant medications – valproate, clonazepam, phenobarbital, haloperidol, thioridazine

Silpakit O, Amornpichetkoon M, Kaojarern S. Comparative study of bioavailability and clinical efficacy of carbamazepine in epileptic patients. Ann Pharmacother. 1997 May;31(5):548-52.

# Results

| | No Seizures | Breakthrough Patients | Total Seizures |
|---|---|---|---|
| Generic 1 | 16/18 | 2/18 | 5 |
| Generic 2 | 11/18 | 7/18 | 14 |
| Generic 3 | 15/18 | 3/18 | 5 |
| Brand | 13/18 | 5/18 | 10 |

- No difference in seizure frequency related to Brand or Generic
- No difference in side-effects
- No difference in patient outcomes

# Conclusions from randomized prospective, controlled studies

- Multi-dose cross-over demonstrates metabolic equivalence between Brand and Generic
- No difference in breakthrough seizures or seizure frequency
- No difference side-effects
- Patients do well on generic anti-epileptic medications

# Clinical Trial Data Support Generic Substitution

- Harvard Systematic Review and Meta-Analysis
  - Looked at 47 studies in cardiovascular therapeutics
  - Included "narrow therapeutic index (NTI)" medications – warfarin and antiarrhythmics
- "The studies in our sample concluded that generic and brand-name cardiovascular drugs are similar in nearly all clinical outcomes."
- "Our results suggest that it is reasonable for physicians and patients to rely on FDA bioequivalence rating as a proxy for clinical equivalence among a number of important cardiovascular drugs, even in higher-risk contexts such as the NTI drug warfarin."

Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. ***JAMA***. 2008 Dec 3;300(21):2514-26.

# Meeting Patients' Needs

- Occasional individual patients might need a branded or specific formulation product
- ***"No substitution" provides the mechanism for those situations***
- For most patients ***access*** to medications is critical
- Generics provide a safe and effective alternative

# Meeting Patients' Needs

- The FDA has the most complete data on the safety and equivalence of generic products
- The FDA process can be relied on to demonstrate that brand and generic products are equivalent
- The published scientific data supports the safety, efficacy and interchangeability of generic products

# Carbamazepine Safety

- Important safety information below
- Please see full prescribing information before prescribing this product

# Carbamazepine
# Brand Name: Tegretol®

- **INDICATIONS AND USAGE**
- **Epilepsy:** Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:
  - Partial seizures with complex symptomatology
  - Generalized tonic-clonic seizures (grand mal).
  - Mixed seizure patterns which include the above, or other partial or generalized seizures.
- **Trigeminal Neuralgia**

# Black Box Warnings

**WARNING**

**SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE**

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY ATRISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS/LABORATORY TESTS**).

# Black Box Warnings

**APLASTIC ANEMIA AND AGRANULOCYTOSIS**

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE CONTROLSTUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

- New HLA data – added December, 2007
- These Adverse Events are NOT dose or formulation related
- Generics and Brand carry identical labeling

# Contraindications

**CONTRAINDICATIONS**

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

# Adverse Reactions

The most severe adverse reactions have been observed in the hemopoietic system (see boxed ***WARNING***), the skin, and the cardiovascular system.
**Hemopoietic System**: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.
**Skin:** Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see ***WARNINGS***), Stevens-Johnson syndrome (see ***WARNINGS***), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
**Cardiovascular System**: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

# Adverse Reactions

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

- More common adverse reactions may be dose related
- Most serious adverse reactions are not dose related