

## Preclinical Testing starts with the discovery of a new molecule

Discovering and developing safe and effective new medicines is a long, difficult and expensive process.

## Preclinical Testing

Pharmacology Toxicology Preformulation

Formulation Analytical Pharmacokinetics

## Time and Expense

Average length of time for testing in non-human subjects takes about 1.5 to 3 years.

The testing is performed in rats, mice and rabbits, etc  
(toxicity and health effects)

Average cost 10 million dollars +

- Some 175000 substances are evaluated annually and about 200 (about 1/1000) actually become new drugs eventually

- Toxicology

- Genetic Toxicology

## What is Genetic Toxicology?

- Study of agents that can alter genes or chromosomes or cause cancer
- The FDA and EPA require certain genetic toxicology assays as part of their safety and risk assessment review

# Use of Genetox Test Results

- To ensure safety of the clinical volunteers
  - Test active ingredient not the final prescribed drug
- Screens out drug candidates that have risks greater than their benefits – most never make it to market
  - Dropped from development for safety or efficacy concerns
- Supports the safety of the ultimately marketed drug product.

**CLARINEX® (desloratadine) TABLETS**

**Brief Summary (For Full Prescribing Information, see package insert.)**

**INDICATIONS AND USAGE:** Allergic Rhinitis: CLARINEX Tablets 5 mg are indicated for the relief of the nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients 12 years of age and older.

**Chronic Idiopathic Urticaria:** CLARINEX Tablets are indicated for the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria 12 years of age and older.

**CONTRAINDICATIONS:** CLARINEX Tablets 5 mg are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, or to loratadine.

**PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of an 18-month study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg/day in mice (estimated desloratadine and desloratadine metabolite exposures were approximately 3 times the AUC in humans at the recommended daily oral dose) and 25 mg/kg/day in rats (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). Male mice given 40 mg/kg/day loratadine had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day and in males and females given 25 mg/kg/day. The estimated desloratadine and desloratadine metabolite exposures of rats given 10 mg/kg/day loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

In genotoxicity studies with desloratadine, there was no evidence of genotoxic potential in a reverse mutation assay (*Salmonella/E. coli* mammalian microsome bacterial mutagenicity assay) or in two assays for chromosomal alterations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

desloratadine doses up to 24 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 4.5 times the AUC in humans at the recommended daily oral dose). A male specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated desloratadine exposures were approximately 45 times the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 8 times the AUC in humans at the recommended daily oral dose).

**Pregnancy Category C:** Desloratadine was not teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 210 times the AUC in humans at the recommended daily oral dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures were approximately 230 times the AUC in humans at the recommended daily oral dose). In a separate study, an increase in pre-implantation loss and a decreased number of implantations and fetuses were noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). Reduced body weight and slow righting reflex were reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 50 times or greater than the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 7 times the AUC in humans at the recommended daily oral dose). There were, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, desloratadine should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Desloratadine passes into breast milk. Therefore a decision should be made whether to discontinue nursing or to discontinue desloratadine, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of CLARINEX Tablets in pediatric patients under 12 years of age have not been established.

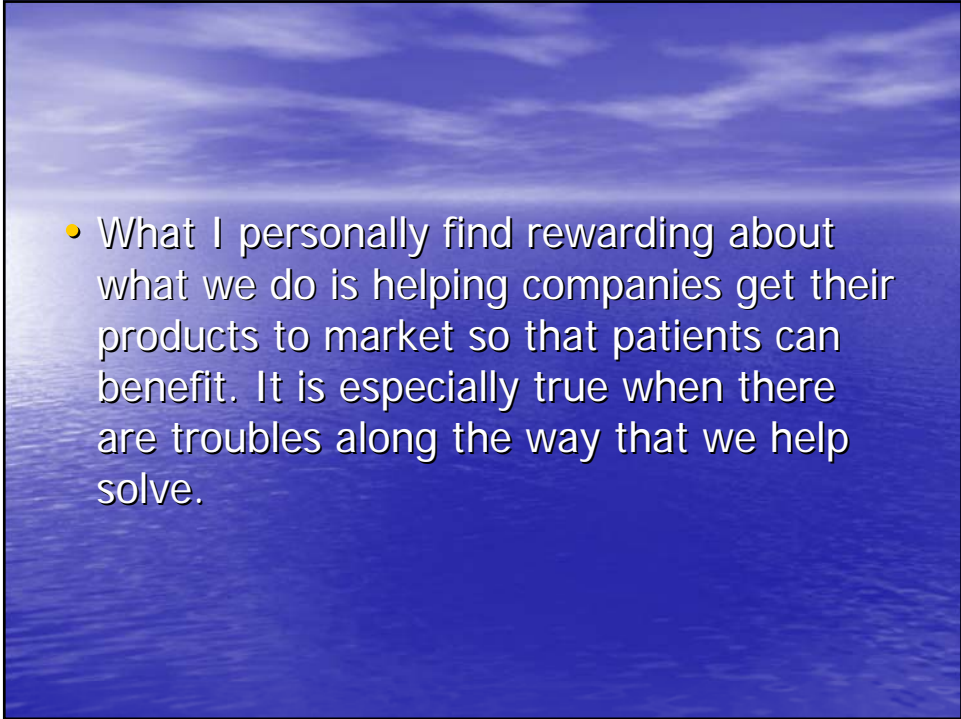
**Geriatric Use:** Clinical studies of desloratadine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from

**Results of GeneTox Tests are provided to patient population**

**From: June 2003 Reader's Digest**

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- What I personally find rewarding about what we do is helping companies get their products to market so that patients can benefit. It is especially true when there are troubles along the way that we help solve.