ACTOS™
(Pioglitazone Hydrochloride) Tablets

Takeda America
Research and Development Center, Inc.
Princeton, New Jersey

Introduction

Roberta L. Schneider, M.D.
Vice President, Drug Development
Takeda America R&D Center, Inc.

ACTOS™ (pioglitazone hydrochloride)

- Is an agent of the thiazolidinedione class
- Evaluated for the treatment of type 2 diabetes mellitus
  - Monotherapy
  - Combination with
    - Sulfonylurea (SU)
    - Metformin
    - Insulin
- Applications to market filed in U.S., Japan, and Europe
- Today's presentation will focus on the safety of ACTOS™

Agenda

- Introduction
  - Roberta L. Schneider, M.D.
- Preclinical Pharmacology and Toxicology
  - Frederick E. Reno, Ph.D.; Consultant
- Clinical Safety Assessment
  - Roberta L. Schneider, M.D.
  - James W. Freston, M.D., Ph.D.; Professor of Medicine and Clinical Pharmacology, Director, Office of Clinical Research, University of Connecticut Health Center
  - Neil Kaplowitz, M.D.; Professor of Medicine, Chief, Division of Gastrointestinal and Liver Diseases, University of Southern California School of Medicine
- Clinical Perspective
  - David E. Kelley, M.D.; Associate Professor of Endocrinology and Metabolism, University of Pittsburgh School of Medicine

Takeda America Research & Development Center, Inc. Representatives

- Drug Development
  - Roberta L. Schneider, M.D.
  - Cindy J. Rubin, M.D.
  - Vincent P. Houser, Ph.D.
  - M. Alyson Spedding
- Statistics and Data Management
  - Annette L. Mathisen, Ph.D.

Consultants Present

- Regulatory Affairs
  - Stephanie D. Rais
- Preclinical
  - Colleen Johnson, M.S., DABT, Toxicology
  - Frederick E. Reno, Ph.D., Toxicology
- Pharmacokinetics
  - Martha Charney, Ph.D.

Consultants Present

- James W. Freston, M.D., Ph.D.
  - Professor of Medicine and Clinical Pharmacology, Director, Office of Clinical Research, University of Connecticut Health Center
- Neil Kaplowitz, M.D.
  - Professor of Medicine, Chief, Division of Gastrointestinal and Liver Diseases, University of Southern California School of Medicine
- David E. Kelley, M.D.
  - Associate Professor of Endocrinology and Metabolism, University of Pittsburgh School of Medicine

Consultants Present

- Hyman J. Zimmerman, M.D.
  - Visiting Scientist, Armed Forces Institute of Pathology Hepatic Department
- Roberto M. Lang, M.D., FACC
  - Professor of Medicine, Director, Noninvasive Cardiac Imaging Laboratories, University of Chicago Medical Center
- Stephen L. Eck, M.D., Ph.D.
  - Assistant Professor of Medicine, University of Pennsylvania School of Medicine
- Keith G. Tolman, M.D.
  - Professor of Medicine, Chief, Hepatology and Clinical Pharmacology, University of Utah School of Medicine

Consultants Present

- Marietta M. Henry, M.S., M.D.
  - Vice President, Medical Affairs, Covance Central Laboratory Services, Inc.
- Samuel M. Cohen, M.D., Ph.D.
  - Professor and Chair, Department of Pathology and Microbiology, University of Nebraska Medical Center
- Michael D. Glant, M.D.
  - Medical Director, Diagnostic Cytology Laboratories

History of ACTOS™

1982 Takeda Chemical Industries, Ltd., Osaka, Japan identified the first thiazolidinedione, ciglitazone

1986 Takeda synthesized pioglitazone

1989 Pioglitazone was licensed to The Upjohn Company, IND submitted, and clinical development initiated

1991 Clinical studies began in Japan

History of ACTOS™

1995 Takeda assumed IND in U.S.

1996 Phase 2/3 clinical studies began in the U.S. and Europe

1999 Takeda submitted NDA No. 21-073 for ACTOS™ (pioglitazone hydrochloride) on January 15

1999 Registration dossier submitted in Europe on March 30

Today's Presentation for ACTOS™

- Preclinical pharmacology and toxicology
- Clinical trial safety data

Pioglitazone Preclinical Pharmacology and Toxicology

Frederick E. Reno, Ph.D.
Consultant in Toxicology

Preclinical Pharmacology

- Pioglitazone lowers glucose levels in obese/diabetic animals
- No hypoglycemic effect in normal animals
- Increases insulin dependent glucose disposal in skeletal muscle
- Decreases hepatic glucose output
- Lowers triglycerides in diabetic and normal animals
- Activates PPAR γ receptors

Preclinical Pharmacokinetics

- Rapid absorption with 81% to 94% bioavailability
- Six metabolites (three are active)
- No liver microsomal enzyme induction or inhibition
- Fecal elimination predominates (except in monkeys)
- Main cytochrome P450 isoforms CYP2C8 and CYP3A4

Cardiac Findings

- Identified in several animal models
- Consistent across thiazolidinedione class
- Threshold effect was primarily increased heart weight
- Threshold dose varied with species
- No change in cardiac function by echocardiography

Hematologic Findings

- Identified in several animal models
- Consistent across thiazolidinedione class
- Threshold effect was decreased RBC parameters
- Threshold dose varied with species
- Changes occurred during early phase of treatment and generally remained stable
- Animals considered physiologically normal

Liver Findings

- Identified in several animal models
- Threshold effect was increased liver weight or the histologic finding of cellular hypertrophy
- Effects consistent with adaptive response to increased metabolic work seen with many different classes of compounds
- Threshold dose varied with species

Threshold Doses for Liver Findings

Species	Dose (mg/kg/day)	Effect
Mouse	3.2	Hepatocellular hypertrophy
	32.0	↑ Liver weight
	320.0	↑ ALT in females
Rat	63.0	Periacinar hepatocytic hypertrophy
	100.0	↑ Liver weight
Dog	10.0	↑ Liver weight; ↑ ALT in males with no histologic changes up to one year
	100.0	Mild subacute hepatitis
	150.0	Atrophy and necrosis
Monkey	8.9	↑ Liver weight
	139.0	↑ Glycogen storage

Duration ≥ 13 weeks

Additional Studies

- Reproduction studies
- Carcinogenicity studies
  - Urinary bladder calculi
- Mutagenicity studies
- Serum lipid studies
- Hepatic microsomal enzyme studies

Reproduction Studies

- Fertility
  - No effect on reproductive performance at 40 mg/kg/day
  - Fetal effects at ≥ 10 mg/kg/day in one study
- Teratology
  - Not teratogenic in rabbits and rats
  - NOEL for fetal effects at 20 mg/kg/day in rats
  - NOEL for fetal effects at 80 mg/kg/day in rabbits
- Perinatal
  - Some delayed development at ≥ 10 mg/kg/day

Carcinogenicity Studies

- No evidence of carcinogenicity in mice
- Calculi-induced tumors of urinary bladder in male rats
- No tumors or preneoplastic lesions of urinary bladder in long-term (1 year) studies of monkey or dog

Preclinical Summary

- Blood glucose lowered in diabetic animals
- Insulin resistance decreased
- Minor hepatic changes, mostly adaptive
- Plasma volume expansion with dilution effects
- Cardiac enlargement in rodents and dogs, but not monkeys

Preclinical Conclusions

- Metabolic benefits related to insulin resistance and glucose homeostasis
- Toxicity is generally consistent with other agents in the class
- No unique toxicity of clinical significance