Cardiovascular & Renal Drugs Advisory Committee

12 December 2007

PULZIUM®

Tedisamil Injection 20 mg/10ml

Solvay Pharmaceuticals

Introduction

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Solvay Pharmaceuticals

Tedisamil
Proposed Indication

The rapid conversion of recent onset (3 hours - 45 days) atrial fibrillation (AFib) or flutter (AFl) to normal sinus rhythm (NSR)

Tedisamil Overview

- Conversion to NSR is rapid and sustained
- Gender-specific dosing
- Robust detection of arrhythmias with Holters
- Favorable benefit-to-risk balance overall, and
  - ≥ 65 years of age
  - Mild-to-moderate renal impairment
  - Receiving beta-blockers
  - Class I - II NHYA congestive heart failure
  - AF of longer duration
- Safe use enhanced by RiskMAP and observational studies

Agenda

Introduction	Victor Raczkowski, MD, MS Solvay Pharmaceuticals
Medical Need	Peter R. Kowey, MD Jefferson Medical College
Efficacy and Safety	Matthias Straub, MD Solvay Pharmaceuticals
Post Marketing Plan	Earl Sands, MD Solvay Pharmaceuticals
Benefit/Risk	Peter R. Kowey, MD Jefferson Medical College
Questions	Victor Raczkowski, MD, MS Solvay Pharmaceuticals

Invited Experts

Peter R. Kowey, MD	William Wikoff Smith Chair in Cardiovascular Research Professor of Medicine and Clinical Pharmacology Jefferson Medical College of Thomas Jefferson University President, Main Line Health Heart Center
Albert L. Waldo, MD	Walter H. Pritchard Professor of Cardiology Professor of Medicine and Professor of Biomedical Engineering Case Western Reserve University

Nonclinical Pharmacology

- Class III anti-arrhythmic drug
- Blocks multiple cardiac potassium currents

  I_{Kr}, I_{Ks}, I_{to}, $I_{K\text{-}ATP}$, I_{Kur}, $I_{K\text{-}ACH}$
- Prolongs cardiac action potential duration
- Prolongs cardiac refractory period
- Decreases heart rate
- Increases blood pressure
- Converts AFib and AFl to NSR in dogs

Clinical Program

- Early clinical development
  - Two-step infusion regimen (2 bags)
  - Gender-specific doses
- Five phase 3 studies
  - Separate studies in males and females
  - Primary endpoint: conversion to NSR
  - Holter monitoring for efficacy and safety
  - 4-week safety monitoring
  - Similar designs allow pooling
  - All positive on primary endpoint

Clinical Program

- Safety database: 931 subjects with AFib/AFl exposed to intravenous tedisamil
- Intensified monitoring to detect arrhythmias
  - Reported by investigators as adverse events, AND
  - Identified by Holter monitoring
- Thorough safety review of Holter recordings
  - Specific definitions for arrhythmias
  - Centrally analyzed
  - Evaluated by Adjudication and Oversight Committee (AOC)

Recommended Use

- Appropriate clinical setting
  - Continuous ECG monitoring
  - Personnel knowledgeable and experienced
- Careful patient selection
- Gender-specific dosing and administration
- Adequate duration of monitoring
  - Two hours from start of infusion, and
  - QTc returns to normal

Benefit/Risk Assessment

- Rapid and sustained conversion to NSR
- Effective and safe in subgroups, including
  - Males and females
  - ≥ 65 years of age
  - Mild-to-moderate renal impairment
  - Receiving beta-blockers
  - NYHA Class I-II congestive heart failure
  - AF of longer duration
- Favorable benefit/risk balance
- Safe use in clinical practice enhanced by RiskMAP and observational studies

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