

Introduction

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Exanta[®] (ximelagatran)— A New Oral Anticoagulant

- ◆ **Ximelagatran**
 - **The first new oral anticoagulant since warfarin approved in 1954**
 - **The first oral treatment in the new drug class: direct thrombin inhibitors**
- ◆ **Mechanism of action different from vitamin K antagonist anticoagulants like warfarin**
- ◆ **Anticoagulation is the major approach to the prevention and treatment of thromboembolism**

Warfarin—the Pros

- ◆ **A highly efficacious anticoagulant**
- ◆ **In top 10 most-prescribed drugs**
- ◆ **3 million patients in USA**
- ◆ **32 million prescriptions in USA**

Warfarin—the Cons

- ◆ **High number of reports for**
 - **Drug interactions**
 - **Medication errors**
 - **Serious bleeding**
 - **Hospital admissions**

- ◆ **Pharmacologic profile of warfarin**
 - **Unpredictable kinetics and dynamics**
 - **Food, alcohol, and multiple drug interactions**
 - **Need for coagulation monitoring/dose titration**

The Thrombin Research Program Target

- ◆ **A new oral anticoagulant and alternative to warfarin with**
 - **Predictable kinetics/dynamics allowing fixed dosing**
 - **No need for coagulation monitoring**
 - **Low risk of food and drug interactions**
 - **Rapid onset and offset of action**
 - **An acceptable bleeding profile**

Ximelagatran Development Program

- ◆ **Worldwide clinical development**
- ◆ **82 clinical studies**
 - > **30,000 persons enrolled**
 - > **17,000 persons received ximelagatran**
 - > **3,500 persons received ximelagatran for more than 1 yr**

Proposed Indications

Proposed indication	Dose, bid	Comparator	Proposed claim and pivotal studies
Long-term secondary prevention of VTE	24 mg	Placebo	Superiority to placebo THRIVE III
Prevention of VTE after knee replacement	36 mg	Warfarin	Superiority to warfarin EXULT A EXULT B
Prevention of stroke in atrial fibrillation	36 mg	Warfarin	Noninferiority to warfarin SPORTIF III SPORTIF V

NDA also includes data from THRIVE VTE Treatment Trial/ ESTEEM phase II dose guiding in post ACS.



Ximelagatran—Benefit Risk Assessment

Effective and predictable
anticoagulation

Favorable bleeding
profile

Patient risk
management

Positive
benefit-risk

Secondary VTE
prevention

VTE prevention in knee
replacement surgery

Stroke prevention
in atrial fibrillation

Ximelagatran—Regulatory History

US IND filed	Aug 1998
NDA submitted	Dec 2003
First approval in France (RMS) (VTE prophylaxis hip/knee)	Dec 2003
MRP completed in 15 countries	May 2004
First launch - Germany	Jun 2004

Agenda

Introduction

Hamish Cameron, MD

Clinical Pharmacology

Troy C. Sarich, PhD

Efficacy

Jay Horrow, MD

Safety

Sunita Sheth, MD

Benefit/Risk Evaluation

Jonathan L. Halperin, MD

Consultants

Gerald Faich, MD, MPH

President, Pharmaceutical Safety Assessments, Inc.

Lloyd Fisher, PhD, FACC

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James H. Lewis, MD, FACP, FACG

Professor of Medicine, Director, Hepatology Georgetown University

Ximelagatran— The First Oral Direct Thrombin Inhibitor

- ◆ **New oral anticoagulant**
- ◆ **Safe and effective alternative to warfarin**
- ◆ **Opportunity to enhance healthcare for life-threatening thromboembolic diseases**