



# **Facilitating Development of Anticoagulant Drugs for Use in Pediatric Patients**

## **FDA Briefing Document**

### **Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)**

**November 2, 2011**

#### **DISCLAIMER STATEMENT**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the topic, “Facilitating Development of Anticoagulant Drugs for Use in Pediatric Patients”, to this Advisory Committee in order to gain the Committee’s insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

## I. Introduction

Recent advances in medical care have increased the number of children requiring anticoagulant therapy. In spite of the increasing use of these anticoagulant agents in pediatric patients, there are few prospective adequate and well-controlled trials to evaluate anticoagulant therapy in this population. Dosing and management for the pediatric population are commonly derived from clinical experience in adults. Although numbers are small relative to use in adult patients, pediatric patients represent an important population in which additional research is needed to better direct clinical use of these agents. Studies of the pharmacokinetics and pharmacodynamics as well as studies evaluating efficacy and safety of anticoagulants in pediatric patients are needed.

Clinical research in pediatric patients poses unique challenges. Among the challenges identified in the evaluation of anticoagulant products in pediatric patients are the following considerations:

- Commercial development of anticoagulant drugs in adults typically addresses thromboprophylactic indications (such as use in patients undergoing major orthopedic surgery) before deep vein thrombosis (DVT)/pulmonary embolism (PE) treatment indications.
- Some aspects of use of the more recently approved anticoagulant products for the treatment of DVT/PE in adults appear problematic in pediatric patients, as the products are approved for use in conjunction with warfarin. Specifically, transition from parenteral low molecular weight heparins (LMWH) to oral warfarin poses challenges as warfarin use may not be standard of care. Warfarin is not approved in pediatric patients and a formulation of warfarin is not available for patients unable to swallow tablets.
- Because the approach to the development of anticoagulant products is sufficiently variable among manufacturers, devising a standard or cohesive approach to obtaining pediatric information for this therapeutic drug group is difficult.

The areas of greatest need for pediatric study of anticoagulants have not been clarified.

The Agency is seeking advice in developing an approach to the study of existing anticoagulant drugs, and of anticoagulant drugs under development, for use in pediatric patient populations.

Questions for Consideration:

1. Indications:
  - a. Which thromboembolic indications should be studied in the pediatric population?

- b. Which age groups should be studied for thromboembolic indications and are there specific study design issues for any particular age group?
  - c. Should anti-coagulants be studied in pediatric populations for prophylactic use and, if so, how should they be studied?
2. Endpoints:
- a. For studies of anticoagulants in pediatric patients, what endpoints should be required?
  - b. Relationship between pharmacodynamic parameters (e.g., INR, anti-Xa levels) and clinical outcome is not precise. What should be the role of pharmacokinetic/pharmacodynamic studies in supporting pediatric indications for anticoagulants?
3. Approaches for products used in conjunction with other anticoagulant agents:
- a. Many of the current anticoagulants have been studied and approved for use in adults in conjunction with warfarin. Should these agents be studied similarly in pediatric populations?
  - b. Are there circumstances where these anticoagulants would be administered as single agents in pediatrics?
  - c. If so, what are the panel's recommendations for study in children?

## II. Background

### **Regulatory Initiatives for Improving Pediatric Labeling**

Historically, children were excluded from clinical trials for numerous reasons and therefore most drug and biological products lacked adequate pediatric information in labeling. Recent pediatric legislation, including a combination of incentives and requirements, has significantly increased pediatric drug research and development and led to a substantial increase in products with new pediatric information in labeling.

The Pediatric Exclusivity provision is an incentive program originally created in the Food and Drug Administration Modernization Act of 1997 (FDAMA), and reauthorized in January 2002, as the Best Pharmaceuticals for Children Act (BPCA). The Pediatric Research Equity Act (PREA), signed into law in December 2003, is a requirement which allows the FDA to require pediatric studies for certain applications. BPCA and PREA

were reauthorized in September 2007, in the Food and Drug Administration Amendments Act (FDAAA), which sunsets on October 1, 2012.

FDAAA requires that the labeling resulting from studies conducted under BPCA and PREA include information on the pediatric studies and a statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations.

The various pediatric initiatives have led to a dramatic increase in pediatric studies submitted to the FDA and resulted in new pediatric information in labeling. There have been almost 400 pediatric labeling changes for drugs and biologics between 1998 and August 2010.

**Best Pharmaceuticals for Children Act (Incentive - Voluntary):** The Pediatric Exclusivity provision allows sponsors to qualify for an additional six months of marketing exclusivity, which attaches to the entire moiety (molecule responsible for the pharmacological action of the drug) not just the drug studied, if the sponsor completes and submits to FDA pediatric studies as outlined in a Written Request. The Pediatric Exclusivity would apply to all of the sponsor's formulations, dosage forms and indications for which the moiety is approved.

A Written Request is a specific document issued by the FDA which outlines the type of studies to be conducted, study design and objectives, and the age groups to be studied. Because the Pediatric Exclusivity provision is voluntary, the sponsor may decline a Written Request. The Pediatric Exclusivity process can be initiated by either the sponsor or the FDA. A sponsor may submit a proposal to the FDA to conduct pediatric studies. If the FDA determines there is a public health need, the Agency will issue a Written Request for pediatric studies. These studies may or may not include the studies proposed by the sponsor. FDA may issue a Written Request on its own initiative when it identifies a need for pediatric data. More than 170 drugs have been granted exclusivity as of August 2010.

Of note, the Pediatric Exclusivity provision originally only applied to drugs.

On March 23, 2010, the Patient Protection and Affordable Care Act which included the "Biologics Price Competition and Innovation Act of 2009" ("Biologics Act") was signed into law. The Biologics Act created a framework for FDA approval of follow-on biologics. The Biologics Act amended section 351 of the Public Health Services Act to make biologics, including follow-on biologics, eligible for Pediatric Exclusivity. The Biologics Act sunsets in March 2015.

**Pediatric Research Equity Act (Requirement):** In December 2003, PREA was signed into law. PREA codified many of the provisions of the Pediatric Rule, a regulation issued by the FDA in December 1998 that required that any new drug application or supplement contain an assessment of the drug or biological product in the pediatric population at the

time of submission, unless a waiver or deferral was granted. The Rule was suspended by court order on October 2002. PREA works in concert with BPCA. In contrast to BPCA, which provides a voluntary mechanism for obtaining needed pediatric studies on either approved or unapproved indications for a given drug, PREA requires pediatric studies but only in the indications for which the sponsor is seeking approval. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. The sponsor must use age appropriate formulations and the studies must include data to support pediatric dosing and administration. Under PREA, pediatric studies of currently marketed drugs and biologics may be required if the product is used by a “substantial” number of children, if adequate pediatric labeling would provide “meaningful” therapeutic benefit compared with existing treatments for children for the claimed indication, or if the lack of “adequate” labeling poses a risk for the pediatric population. PREA does not apply to products granted orphan designation.

Pediatric studies are often started after adult studies are complete. Therefore, most pediatric studies are not submitted when the product is initially approved in adults. Discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the product development process. Pediatric studies may be deferred (postponed until a later date) by the FDA in certain situations including if the application is ready for approval for use in adults before pediatric studies are complete, or when additional safety or effectiveness data needs to be collected before studying in the pediatric population. Studies may be waived (requirement released) in full or in part in certain situations, including when necessary studies are impossible or highly impracticable, there is evidence strongly suggesting that the product would be ineffective or unsafe in all or some pediatric age groups or the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

### **Current Pediatric Labeling for Anticoagulant Products**

Information for use of a product in pediatric patients may be found in a number of places within drug labeling. The location of the information is dependent on whether the product is approved for use in pediatrics and the safety profile of the drug. In general, if a drug is not approved for use in pediatric patients information will be located in section 8.4, Use in Specific Populations; Pediatric Use. Other sections of labeling may include information relevant to use in pediatric patients as appropriate. For example, safety information may be located in Contraindications or Warnings and Precautions. For products approved in pediatric patients; information is typically distributed throughout the labeling as appropriate.

The first anticoagulant marketed in the U.S. was heparin sodium which was approved in 1939, prior to current New Drug Application (NDA) rules. Following passage and implementation of the efficacy amendments (Harris-Kefauver Amendments) to the Food, Drug and Cosmetic Act in 1962, the safety and efficacy of heparin products was reviewed by the National Academy of Sciences under the Drug Efficacy Study

Implementation (DESI) process during the 1960s and 1970s and the currently labeled indications including treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) were established. Updated guidelines for heparin sodium labeling were published in the Federal Register in 1983. The labeling for the most recently approved heparin sodium product (Pfizer, 7/21/2011) contains the following wording regarding dosing in pediatric patients:

- **Use in Specific Populations: 8.4 Pediatric Use**  
There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience [*see Dosage and Administration (2.4)*].
- **Dosage and Administration: 2.4 Pediatric Use**  
Use preservative-free HEPARIN SODIUM INJECTION in neonates and infants.

There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience. In general, the following dosage schedule may be used as a guideline in pediatric patients:

Initial Dose: 75 to 100 units/kg (IV bolus over 10 minutes)

Maintenance Dose: Infants: 25 to 30 units/kg/hour;  
Infants < 2 months have the highest requirements  
(average 28 units/kg/hour)

Children > 1 year of age: 18 to 20 units/kg/hour;  
Older children may require less heparin, similar to  
weight-adjusted adult dosage

Monitoring: Adjust heparin to maintain aPTT of 60 to 85 seconds, assuming  
this reflects an anti-Factor Xa level of 0.35 to 0.70

The orally administered anticoagulant Coumadin (warfarin sodium) was first approved in the U.S. in 1954. It is broadly labeled for the prophylaxis and/or treatment of venous thrombosis and its extension. It also is labeled for cardiac indications (prevention of stroke in non-valvular atrial fibrillation, use in patients after MI). The current pediatric use information in the label (approved 10/04/2011) is as follows:

**Use in Specific Populations: 8.4 Pediatric Use:** Adequate and well-controlled studies with COUMADIN have not been conducted in any pediatric population, and the optimum dosing, safety, and efficacy in pediatric patients is unknown. Pediatric use of COUMADIN is based on adult data and recommendations, and available limited pediatric data from observational studies and patient registries. Pediatric patients administered COUMADIN should avoid any activity or sport that may result in traumatic injury. The developing hemostatic system in infants and children results in a changing physiology of thrombosis and response to anticoagulants. Dosing of warfarin in the pediatric population varies by patient age, with infants generally having the highest, and adolescents having the lowest milligram per kilogram dose requirements to maintain target INRs. Because of changing warfarin requirements due to age, concomitant medications,

diet, and existing medical condition, target INR ranges may be difficult to achieve and maintain in pediatric patients, and more frequent INR determinations are recommended. Bleeding rates varied by patient population and clinical care center in pediatric observational studies and patient registries. Infants and children receiving vitamin K-supplemented nutrition, including infant formulas, may be resistant to warfarin therapy, while human milk-fed infants may be sensitive to warfarin therapy. Pediatric dosing recommendations are based on clinical experience [see *Dosage and Administration* (2.4)].

Other marketed parenteral anticoagulants include low molecular weight heparins (LMWH) [i.e., Lovenox (enoxaparin sodium), Fragmin (dalteparin sodium), Innohep (tinzaparin sodium), Arixtra (fondaparinux sodium)] and thrombin inhibitors [i.e., argatroban, Angiomax (bivalirudin), Refludan (lepirudin)]. The pediatric use information for these products is summarized in the following table.

<b>Drug</b>	<b>Approved Indications</b>	<b>Pediatric Use Information</b>
Lovenox (enoxaparin sodium)	Treatment of DVT/PE when administered in conjunction with warfarin sodium; DVT/PE thromboprophylaxis in: knee replacement surgery hip replacement surgery, abdominal surgery, and medical patients with restricted mobility; unstable angina and non-Q-wave myocardial infarction (MI); acute ST elevation MI	<b>8.4 Pediatric Use</b> Safety and effectiveness of Lovenox in pediatric patients have not been established.
Fragmin (dalteparin sodium)	DVT/PE thromboprophylaxis in: hip replacement surgery and abdominal surgery, and medical patients with restricted mobility; extended treatment of VTE in patients with cancer; unstable angina and non-Q-wave myocardial infarction (MI)	<b>8.4 Pediatric Use</b> Safety and effectiveness in pediatric patients have not been established.
Innohep (tinzaparin sodium)	Treatment of acute symptomatic DVT with or without PE when administered in conjunction with warfarin sodium	<b>Pediatric Use:</b> Safety and effectiveness of tinzaparin sodium in pediatric patients have not been established.

<p>Arixtra (fondaparinux sodium)</p>	<p>Treatment of DVT/PE when administered in conjunction with warfarin sodium; DVT/PE thromboprophylaxis in: knee replacement surgery, hip replacement surgery, hip fracture surgery, and abdominal surgery</p>	<p><b>8.4 Pediatric Use</b> Safety and effectiveness of ARIXTRA in pediatric patients have not been established. Because risk for bleeding during treatment with ARIXTRA is increased in adults who weigh &lt;50 kg, bleeding may be a particular safety concern for use of ARIXTRA in the pediatric population [see Warnings and Precautions (5.3)].</p>
<p>Argatroban</p>	<p>Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT); in patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)</p>	<p><b>Pediatric Use:</b> The safety and effectiveness of Argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients.... <i>[This section includes a comment recommending reduced dose in pediatric patients given argatroban, based on safety information from a study of argatroban among seriously ill pediatric patients who required an alternative to heparin anticoagulation where increased bleeding risk was seen in patients with hepatic impairment].</i></p>
<p>Angiomax (bivalirudin)</p>	<p>In patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA); with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) in patients undergoing percutaneous coronary intervention (PCI); for patients with, or at risk of, HIT or HIT with thrombosis syndrome (HITTS) undergoing PCI.</p>	<p><b>8.4 Pediatric Use</b> The safety and effectiveness of Angiomax in pediatric patients have not been established.</p>

Refludan (lepirudin)	in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications	<b>Pediatric Use</b> Safety and effectiveness in pediatric patients have not been established. <i>[This section also includes descriptive information from literature about 2 children (11 and 12 yrs) who received lepirudin and had no serious adverse event].</i>
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There are two other recently approved orally administered anticoagulants are:

- Pradaxa (dabigatran), which was approved 10/19/2010 to reduce risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation. The Pediatric Use section of the labeling includes the pediatric disclaimer language.
- Xarelto (rivaroxaban), which was approved 7/01/2011, for the indication thromboprophylaxis in patients undergoing knee or hip replacement surgery; The Pediatric Use section of the labeling includes the pediatric disclaimer language.

Three of the anticoagulant products have postmarketing requirements for studies of pediatric patients under the Pediatric Research Equity Act (PREA):

<b>Product</b>	<b>PREA Requirement</b>
Fragmin (dalteparin sodium)	To evaluate efficacy and safety of dalteparin in pediatric cancer patients. Studies using dalteparin for venous thromboembolism (VTE) treatment in all age ranges of the pediatric population should be performed.
Arixtra (fondaparinux sodium)	Treatment of acute deep vein thrombosis and acute pulmonary embolism when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years
Innohep (tinzaparin sodium)	Treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium in hospitalized patients in pediatric patients ages 0-16.

### **Written Requests (WRs)**

Written Requests have been issued for some agents and have resulted in the placement of pediatric safety information in the label. An example of this is for argatroban. To date, no anticoagulant products have received a labeled indication for use in pediatric patients.

## **III. Discussion**

Pediatric patients represent a population where there is widespread use and a clear therapeutic need for anticoagulants. Current practice is informed mainly by experience with these agents in adult patients. FDA initiatives to encourage clinical investigations of anticoagulant drugs in pediatric patients have generally not generated adequate information to support a pediatric indication or inclusion of pediatric dosing recommendations in product labeling.

The primary objective of this subcommittee meeting is to advance the development of anticoagulant drugs for pediatric use by gathering information and fostering communication between FDA, academicians, and industry. The Agency seeks to better understand the challenges to developing anticoagulant drugs for pediatric patients and identify strategies to encourage and facilitate studies that will result in addition of substantive information to product labels to optimize anticoagulant therapy in children.