

Division Director's Review

NDA: 20-883
Product: Argatroban Injection
Sponsor: Encysive Pharmaceuticals, Inc.
Today's date: May 2, 2008
Submission date: August 16, 2007 initiated the second cycle review of this supplement which is intended to provide pediatric use information within the label

1. Main point:

This supplemental NDA provides important new pediatric use information within the product label and I concur with the approval. The label revision does not revise the product's indication; instead, important dosing information is provided for use by clinicians in situations where they choose to use Argatroban among seriously ill pediatric patients. We have also denied the request for pediatric exclusivity (consistent with prior denial).

2. Background:

Argatroban is an arginine derivative/direct thrombin inhibitor approved for use as an anticoagulant in the prophylaxis or treatment of heparin-induced thrombocytopenia (HIT) as well as for use "in patients with or at risk for HIT undergoing percutaneous coronary intervention. This specific supplemental NDA submission contained pharmacokinetic/pharmacodynamic (PK/PD) and clinical data from a pediatric study and was intended to support addition of pediatric labeling information to the label.

Time line:

June 30, 2000	Approval; letter included a PMC "to conduct PK and safety studies in pediatric patients to allow for appropriate dosing instructions in this population."
March 19, 2004	FDA issues Written Request (WR) for pediatric studies
April 7, 2005	FDA issues a revised WR for pediatric studies ("outcomes and PK/PD"
June 29, 2005	Encysive submits a pediatric supplement and request for pediatric exclusivity determination; the exclusivity was denied
September 27, 2005	Pediatric exclusivity denied; internal recommendation memo from Pediatric Exclusivity Board
December 21, 2005	FDA issues approvable letter for the supplement

August 16, 2007 Encysive submits this supplement/response to December 21, 2005
approvable letter; cover letter also requests a pediatric exclusivity
determination and documentation of fulfillment of the pediatric
PMC (from 2000)

3. Application content:

Encysive submitted extensive PK/PD data from a study that enrolled 18 seriously ill pediatric patients (including eight less than six months of age). These data were used in modeling analyses by the Clinical Pharmacology Biometrics review group to provide persuasive evidence that the initial, continuous infusion dose of Argatroban should be much lower (0.75 mcg/kg/min) for seriously ill pediatric patients than the dose recommended for adults (2.0 mcg/kg/min) in the product label.

Although the sample size for the clinical study precluded (as anticipated) the ability to identify a full therapeutic regimen, the detection of an important initial dosage consideration provides useful safety information. This initial dosage information is useful even in the absence of full therapeutic regimen information since Argatroban dosages are subsequently titrated to achieve specific anticoagulation goals (following the initiation of the drug)—i.e., in the general use of argatroban, identification of the initial infusion dose is among the most important safety considerations.

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/s/

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