APPLICATION NUMBER:

203049Orig1s000

PHARMAKOLOGY REVIEW(S)
PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203-049
Supporting document/s: Electronic submission (SDN-001)
Applicant's letter date: March 18, 2011
CDER stamp date: March 21, 2011
Product: Argatroban Injection
Indication: Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; also in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention
Applicant: Hikma Pharmaceutical Co., Ltd.
Review Division: Division of Hematology and Oncology Toxicology (DHOT), for Division of Hematology Products (DHP)
Reviewer: Shwu-Luan Lee, Ph.D.
Supervisor/Team Leader: Haleh Saber, Ph.D.
Division Director: John Leighton, Ph.D. (DHOT)
Ann Farrell, MD (DHP)
Project Manager: Lara Akinsanya

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1 Executive Summary

1.1 Recommendations

There are no pharmacology/toxicology issues which preclude the approval of Argatroban Injection for the intended indication.

1.1.1 Approvability

Recommending approval.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The content of the nonclinical sections of the label is similar to that of the reference listed drug (RLD). Changes are made to the label based on the most recent practices and to comply with 21CFR201.56 and 21CFR201.57 on PLR formatting. These changes are reflected in the following sections: 8.1 Pregnancy; 8.3 Nursing Mothers; 12.1 Mechanism of Action; 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

1.2 Brief Discussion of Nonclinical Findings

The efficacy and safety evaluation of Argatroban Injection are relied on the FDA finding of safety or effectiveness for the RLD (NDA 20883), as described in the drug’s approved labeling.

The safety of propylene glycol (PG) in undiluted drug product, i.e., % w/v (or % v/v), was assessed by a single dose study in dogs (summary of a published reference) and clinical study data (including an article by Wilson et al., 2005). The content of PG is within the range of the PG content (up to 80% v/v) in FDA approved drugs. The level of PG in the drug product is acceptable.

2 Drug Information

2.1 Drug
2.1.1 CAS Registry Number (Optional)
141396-28-3

2.1.2 Generic Name
N/A

2.1.3 Code Name
N/A

2.1.4 Chemical Name
1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate.

2.1.5 Molecular Formula/Molecular Weight
C_{23}H_{36}N_{6}O_{5}S\cdot H_{2}O/526.66

2.1.6 Structure

2.1.7 Pharmacologic class
Direct thrombin inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s
Reference listed drug: NDA 20883 (Pfizer).

2.3 Clinical Formulation
2.3.1 Drug Formulation

The composition of Argatroban Injection, 100 mg/mL (250 mg/2.5 mL) is provided in the table below (from the Applicant).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Function of Components</th>
<th>Concentration (mg/mL)</th>
<th>Content per vial (mg/Vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Active Pharmaceutical Ingredient</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>Propylene Glycol, USP</td>
<td></td>
<td>(b)(c)</td>
<td>1300</td>
</tr>
<tr>
<td>Dehydrated Alcohol, USP</td>
<td></td>
<td>(b)(c)</td>
<td>800</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td></td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

A summary of excipients and their inactive ingredient grade (IIG) limits is described in the following table:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>IIG Levels¹</th>
<th>Concentration mg/mL</th>
<th>Content per Vial (mg/Vial)</th>
<th>Content % (%/Vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene Glycol, USP</td>
<td>IM-IV; Injection 82.04%</td>
<td>(b)(c)</td>
<td>1300</td>
<td>(b)(c)</td>
</tr>
<tr>
<td>Dehydrated Alcohol, USP</td>
<td>Intravenous (Infusion); Injection 80%</td>
<td>(b)(c)</td>
<td>800</td>
<td>(b)(c)</td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>N/A</td>
<td>(b)(c)</td>
<td>(b)(c)</td>
<td>(b)(c)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>(b)(c)</td>
<td>(b)(c)</td>
<td>100</td>
</tr>
</tbody>
</table>


As noted in the table above, the amount of propylene glycol (% w/v) is smaller than IIG (inactive ingredient grade) limits. The amount of dehydrated alcohol in this Applicant’s argatroban is also within the range reported in IIG. See the discussion regarding the content of propylene glycol under Section 2.3.2.

Comparison of drug product to the RLD (table from the Applicant); “Exela” refers to Argatroban Injection by Hikma.
### Ingredients

<table>
<thead>
<tr>
<th></th>
<th>Exela’s Formulation</th>
<th>Pfizer’s Formulation&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each vial contains: (in mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Dehydrated Alcohol, USP</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>D-Sorbitol USP</td>
<td></td>
<td>750</td>
</tr>
<tr>
<td>Propylene Glycol, USP</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>Water for Injection, USP</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

<sup>1</sup> Information regarding Pfizer’s Argatroban formulation was obtained from the current package insert, vial label and carton.

Qualitative differences between the two formulations include reduced amount of dehydrated alcohol<sup>2</sup> and removal of D-sorbitol from the RLD formulation, and the addition of propylene glycol<sup>3</sup>.

The impurity specification of the drug product (DP) is provided in the Appendix.

#### 2.3.2 Comments on Novel Excipients

There are no novel excipients. Below is a discussion on the level of propylene glycol.

The content of the excipient, propylene glycol (PG) in undiluted drug product is approximately<sup>4</sup> w/v (i.e.,<sup>5</sup>) or v/v<sup>6</sup> PG/mL, based on the density of PG<sup>7</sup>. The drug will be diluted 100-fold before administration, resulting in a<sup>8</sup> PG solution. This level is smaller than levels in FDA approved intravenous products (e.g., lorazepam contains<sup>9</sup>; diazepam contains<sup>10</sup>).

The Applicant refers to a clinical research where patients (n=21) in the ICU received IV benzodiazepine delivered in propylene glycol (such as lorazepam or diazepam) versus patients (n=23) receiving benzodiazepine delivered in an alternative<sup>11</sup> (such as midazolam) (Wilson et al., Chest, 128: 1674-1681, 2005). According to this article, propylene glycol appeared to be safe when given intravenously at up to approximately 1 g/kg/day. In another article (Yahwak et al., Pharmacotherapy 28: 984-991, 2008), PG-related toxicities are suggested at above 0.4 g/kg/day. The highest infusion rate of argatroban is 30 mcg/kg/min based on the label. This will be 0.0432 g/kg/day of argatroban (2.6 g/day, or 26 mL undiluted drug product, based on an average body weight of 60 kg). Thus at the highest level dose of argatroban it will deliver about 13.5 g/day (0.52 g/mL PG x 26 mL) or 0.23 g/kg/day of PG, an amount smaller than 0.4 g/kg/day. The Applicant also provides a summary table regarding safety of intravenous PG in patients, based on the studies of intravenous Lorazepam (Table 8, Module 2, Section 2.7.4, Page 13; data not shown).
The proposed level of PG is acceptable from a safety perspective. PG may affect the clotting endpoints(s); see below Section 6.1. The acceptability of the PG level with regard to efficacy endpoints is deferred to the medical team.

2.3.3 Comments on Impurities/Degradants of Concern

2.4 Proposed Clinical Population and Dosing Regimen

- For prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT)
- As an anticoagulant for adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI)
2.5 Regulatory Background


3 Studies Submitted

3.1 Studies Reviewed


3.2 Studies Not Reviewed

No studies are included in this submission.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

N/A

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

N/A
5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

The Applicant submits an article (Influence of pentobarbital sodium anesthesia on hematologic values in the dog; Gentry and Black, Am. J. Vet. Res. 37(11): 1349-1352, 1976), where the effects of propylene glycol (PG) (and pentobarbital) on hematologic parameters, including erythrocyte hemolysis and blood coagulation variables, was assessed in a toxicity study in female dogs. Two doses of compounds (see table below) were administered to animals with a 7-day washout period in between. The blood samples were collected at 0, 5, 10, 60, 180 and 360 minute intervals.

The study design is summarized in the table below: table from the Applicant.

<table>
<thead>
<tr>
<th>Species</th>
<th>Treatment Arms</th>
<th>Dosage</th>
<th>Duration</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Comercial pentobarbital Sodium (60 mg/ml with 40% PG and 10% ethanol)</td>
<td>1 ml/2.27 kg of body weight</td>
<td>2 min</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>40 % PG in sterile saline solution</td>
<td>1 ml/2.27 kg of body weight</td>
<td>2 min</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pentobarbital sodium (60 mg/ml of sterile saline solution)</td>
<td>1 ml/2.27 kg of body weight</td>
<td>2 min</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10% ethanol in sterile saline solution</td>
<td>1 ml/2.27 kg of body weight</td>
<td>2 min</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Sterile saline solution (Control)</td>
<td>1 ml/2.27 kg of body weight</td>
<td>2 min</td>
<td>8</td>
</tr>
</tbody>
</table>

• Results:

Reference ID: 3042191
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Noteworthy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Hemoglobin</td>
<td>• Both commercial pentobarbital sodium and the 40% PG solution caused statistically significant increase in plasma hemoglobin content (P &lt; 0.10).</td>
</tr>
</tbody>
</table>
| Whole blood-clotting time (WBCT)     | • A decrease in WBCT occurred up to 60 min after the commercial pentobarbital sodium administration (P < 0.05).  
• The 40% PG solution decreased WBCT up to 30 min. |
| Partial thromboplastin time (PTT)    | • Significant decrease in PTT assay at 10, 30, 60 min occurred after administration of the commercial pentobarbital sodium solution (P < 0.05).  
• An immediate but transient shortening of the PTT (at 5 and 10 min) occurred after administration of 40% PG solution. |
| Extrinsic coagulation system         | • No evidence of changes                                                              |
| Whole blood clot retraction and platelet counts | • No evidence of changes                                                              |

In summary, the commercial pentobarbital and 40% PG caused erythrocyte hemolysis (indicated as increased plasma hemoglobin), and decreased whole blood clotting time (WBCT) and partial thromboplastin time (PTT) (which may suggest increased procoagulant activity involving the intrinsic coagulation system).

**Reviewer’s note:** It is important to mention that the argatroban vial will be diluted 100-fold prior to administration. Thus, the PG administered is \[\text{[Redacted]}\] as indicated in the concentrated drug product vial. It is not known whether the PG will affects the clotting endpoints.

The following figures depict the findings in details (according to individual parameters):

- Effect of experimental treatments on the plasma hemoglobin:
Effect of Experimental Treatments on the Whole Blood Clotting Time (WBCT)

Fig 1—The effect of various preparations on the plasma hemoglobin, expressed as percentage change. Commercial pentobarbital sodium (60 mg of sodium salt/ml with 40% propylene glycol, n = 8 dogs (-----)); 40% propylene glycol in sterile saline solution, n = 4 dogs (-----); pentobarbital sodium (60 mg/ml of sterile saline solution), n = 8 dogs (-----); 10% ethanol in sterile saline solution, n = 4 dogs (-----); sterile saline solution control, n = 8 dogs (-----).
Effect of Experimental Treatments on Partial Thromboplastin Time (PTT) Assays

Fig 2—The effect of various preparations on the whole blood clotting time (WBCT), expressed as percentage change. Commercial pentobarbital sodium (60 mg of sodium salt/ml with 40% propylene glycol), n = 8 dogs (--- --- ---); 40% propylene glycol in sterile saline solution, n = 4 dogs (-----); pentobarbital sodium (60 mg/ml of sterile saline solution), n = 8 dogs (-------); 10% ethanol in sterile saline solution, n = 4 dogs (--------); sterile saline solution control, n = 8 dogs (--------).
6.2 Repeat-Dose Toxicity

N/A

7 Genetic Toxicology

N/A

7 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

9.1 Fertility and early embryonic development

N/A
9.2 Embryonic Fetal Development
N/A

10 Special Toxicology Studies
N/A

11 Integrated Summary and Safety Evaluation

This submission is a 505(b)(2) NDA. The efficacy and safety evaluation of argatroban in the present submission is based on the FDA finding of safety or effectiveness for the RLD (NDA 20883), as described in the drug’s approved labeling.

The non-clinical and clinical data for justification of propylene glycol (PG) content in the drug product are reviewed. Since the content is within the range of PG levels in FDA approved drugs (up to 80% v/v), and the drug product will be diluted 100-fold upon administration, the level of PG in the drug product is acceptable from a safety standpoint. High concentrations of PG affected coagulation endpoints in animals. The acceptability of the PG level in the drug product with regard to efficacy endpoints is deferred to the medical team.

12 Appendix/Attachments

Applicant's proposal: Specification of drug substance
Specification and acceptance criteria:
Summary of Applicant's Drug Substance Test Results

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHWU LUAN LEE
12/01/2011

HALEH SABER
12/01/2011
**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement**

**NDA/BLA Number:** 203049  
**Applicant:** Hikma Pharmaceutical Co. Ltd  
**Stamp Date:** March 28, 2011  
**Drug Name:** Argatroban  
**NDA/BLA Type:** 505(b)2

On **initial** overview of the NDA/BLA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?</td>
<td>x</td>
<td></td>
<td>Pharmacology/toxicology data including two reports to assess clinical safety of high content of propylene glycol in the drug product (a summary of a single dose toxicology study in dogs; clinical safety summary) were submitted.</td>
</tr>
<tr>
<td>2 Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Is the pharmacology/toxicology section legible so that substantive review can begin?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?</td>
<td>x</td>
<td></td>
<td>The two no-clinical studies (see above) were not GLP compliant. However, this is acceptable as the studies are not considered pivotal.</td>
</tr>
</tbody>
</table>

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 2945542
<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?</td>
<td>x</td>
<td></td>
<td>Using RLD package insert as the template.</td>
</tr>
<tr>
<td>10. Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)</td>
<td></td>
<td></td>
<td>Pending CMC review.</td>
</tr>
<tr>
<td>11. Has the applicant addressed any abuse potential issues in the submission?</td>
<td></td>
<td></td>
<td>Not applied</td>
</tr>
<tr>
<td>12. If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?</td>
<td></td>
<td></td>
<td>Not applied</td>
</tr>
</tbody>
</table>

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shwu-Luan Lee, Ph.D.  
5/5/2011  
Reviewing Pharmacologist  

Team Leader/Supervisor  

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement  
010908

Reference ID: 2945542
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHWU LUAN LEE
05/11/2011

HALEH SABER
05/12/2011