Argatroban Injection

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Argatroban injection is indicated for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT). (1.1)

1.2 Pericarditis Coronary Intervention

Argatroban injection is indicated as an anticoagulant in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI). (1.2)

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Discard unused final product at the completion of these post dilution storage periods. Prepared solutions should not be exposed to direct sunlight. No significant potency losses have been noted following simulated delivery of the solution through intravenous tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2.2 Dosing in Patients with Heparin-Induced Thrombocytopenia

Initial Dose: Before administering argatroban injection, discontinue heparin therapy and obtain a baseline aPTT. The recommended initial dose of argatroban injection for adult patients without hepatic impairment is 2 mcg/kg/min, and check the ACT 5 to 10 minutes later (see Table 4).

Recommended Dose Adjustments of Argatroban Injection for Patients Outside Recommended Range

Table 4 Recommended Doses and Infusion Rates for 2 mcg/kg/min Dose of Argatroban Injection for Patients without Hepatic Impairment

<table>
<thead>
<tr>
<th>Initial Dose (mcg/kg/min)</th>
<th>Recommended Dose (mcg/kg/min)</th>
<th>Infusion Rate (mcg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>1.5</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>2.0</td>
<td>2.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 2 Recommended Storage Conditions of Diluted Solution

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Storage Limit</th>
<th>Storage Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Sodium Chloride Injection</td>
<td>96 hours</td>
<td>20 to 25°C (68 to 77°F)</td>
</tr>
<tr>
<td>5% Dextrose Injection or Lactated Ringer’s Injection</td>
<td>4 hours</td>
<td>2 to 8°C (36 to 46°F)</td>
</tr>
</tbody>
</table>

*with or without thrombosis

Monitoring Therapy:
For use in HIT, therapy with argatroban injection is monitored using the aPTT with a target range of 1.5 to 3.0 times the initial baseline value (not to exceed 100% seconds). Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1 to 3 hours following initiation of argatroban injection. Check the aPTT 2 hours after each additional bolus or change in the rate of infusion.
following initiation of argatroban injection. Check the aPTT 2 hours after initiation of therapy and after any dose change to confirm that the patient has attained the desired therapeutic range.

2.4 Dosing in Patients with Hepatic Impairment

Initial Dosing

For adult patients with HIT or moderate to severe hepatic impairment (based on Child-Pugh classification), an initial dose of 0.5 mg/kg/h should be administered as a large bolus intravenous dose over 3 to 5 minutes (see Table 3). Check the activated clotting time (ACT) 5 to 10 minutes after the bolus dose is completed. The PGI procedure may proceed if the ACT is greater than 700 seconds.

Dose Adjustment

If the ACT is less than 300 seconds, an additional intravenous bolus dose of 150 mcg/kg should be administered, followed by a continuous infusion of 30 mcg/kg/h and the ACT should be checked 5 to 10 minutes later (see Table 4).

If the ACT is greater than 450 seconds, decrease the infusion rate to 15 mcg/kg/h, and check the ACT 5 to 10 minutes later (see Table 4). Continue to monitor the dose until therapeutic ACT (between 300 and 450 seconds) has been achieved; continue the same infusion rate for the duration of the PGI procedure.

In the absence of discrete, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150 mcg/kg may be administered and the infusion dose increased to 40 mcg/kg/h. Check the ACT after each additional bolus or change in the rate of infusion.

Table 2

Recommended Starting and Maintenance Doses (Within the Target ACT Range) of Argatroban Injection in Patients Undergoing PCI Without Hepatic Impairment (1 mg/mL, Final Concentration)

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Bolus Dose (mcg)</th>
<th>Bolus Volume (mL)</th>
<th>Continuous Infusion Dose (mcg/min)</th>
<th>Continuous Infusion Rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>17.50</td>
<td>18</td>
<td>1.250</td>
<td>150</td>
</tr>
<tr>
<td>60</td>
<td>21.00</td>
<td>21</td>
<td>1.500</td>
<td>170</td>
</tr>
<tr>
<td>70</td>
<td>24.50</td>
<td>25</td>
<td>1.750</td>
<td>190</td>
</tr>
<tr>
<td>80</td>
<td>28.00</td>
<td>28</td>
<td>2.000</td>
<td>210</td>
</tr>
<tr>
<td>90</td>
<td>31.50</td>
<td>32</td>
<td>2.250</td>
<td>230</td>
</tr>
<tr>
<td>100</td>
<td>35.00</td>
<td>35</td>
<td>2.500</td>
<td>250</td>
</tr>
<tr>
<td>110</td>
<td>38.50</td>
<td>39</td>
<td>2.750</td>
<td>270</td>
</tr>
<tr>
<td>120</td>
<td>42.00</td>
<td>42</td>
<td>3.000</td>
<td>290</td>
</tr>
<tr>
<td>130</td>
<td>45.50</td>
<td>46</td>
<td>3.250</td>
<td>310</td>
</tr>
<tr>
<td>140</td>
<td>49.00</td>
<td>49</td>
<td>3.500</td>
<td>330</td>
</tr>
</tbody>
</table>

NOTE: 1 mg = 1,000 mcg; 1 kg = 2.2 lbs

Table 4

Recommended Dose Adjustments of Argatroban Injection for Patients Outside of ACT Target Range During PCI Without Hepatic Impairment (1 mg/mL, Final Concentration)

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Continuous Infusion Dose (mcg/min)</th>
<th>Continuous Infusion Rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>7.50</td>
<td>1,500</td>
</tr>
<tr>
<td>60</td>
<td>9.00</td>
<td>1,800</td>
</tr>
<tr>
<td>70</td>
<td>10.50</td>
<td>2,100</td>
</tr>
<tr>
<td>80</td>
<td>12.00</td>
<td>2,400</td>
</tr>
<tr>
<td>90</td>
<td>13.50</td>
<td>2,700</td>
</tr>
<tr>
<td>100</td>
<td>15.00</td>
<td>3,000</td>
</tr>
<tr>
<td>110</td>
<td>16.50</td>
<td>3,300</td>
</tr>
<tr>
<td>120</td>
<td>18.00</td>
<td>3,600</td>
</tr>
<tr>
<td>130</td>
<td>19.50</td>
<td>3,900</td>
</tr>
<tr>
<td>140</td>
<td>21.00</td>
<td>4,200</td>
</tr>
</tbody>
</table>

NOTE: 1 mg = 1,000 mcg; 1 kg = 2.2 lbs

2.5 Dosing in Pediatric Patients with Heparin-Induced Thrombocytopenia/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome

Initial Dosing

Initial argatroban injection infusion doses are lower for seriously ill pediatric patients compared to adults with normal hepatic function [see Use in Specific Populations (8.4)].

Monitoring Therapy

In general, therapy with argatroban injection is monitored using the aPTT. Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within one to three hours after initiation of argatroban injection in patients without hepatic impairment [see Warnings and Precautions (5.2)]. Dosing adjustments may be required to attain the target aPTT. Check the aPTT two hours after initiation of therapy and after any dose change to confirm that the patient has attained the desired therapeutic range.

Dose Adjustment

[see Use in Specific Populations (8.4)].

2.6 Conversion to Oral Anticoagulant Therapy

Initiating Oral Anticoagulant Therapy

When converting patients from argatroban injection to oral anticoagulant therapy, consider the potential for combined effects on INR with co-administration of argatroban and warfarin. A loading dose of warfarin should not be used. Initiate therapy using the expected daily dose of warfarin. To avoid prothrombotic effects and to ensure continuous anticoagulation when initiating warfarin, it is suggested that argatroban and warfarin therapy be overlapped. There are insufficient data available to recommend the duration of the overlap.

Co-Administration of Warfarin and Argatroban Injection at Doses up to 2 mcg/kg/min:

Measure INR daily while argatroban injection and warfarin are co-administered. In general, with doses of argatroban up to 2 mcg/kg/min, argatroban injection can be discontinued when the INR is greater than 4 on 3-4 combined therapy. After argatroban injection is discontinued, discontinue the INR measurement in 4 to 6 hours. If the repeat INR is below the desired therapeutic range, heparin infusion be resumed.

Co-Administration of Warfarin and Argatroban Injection at Doses Greater than 2 mcg/kg/min:

For doses of argatroban injection greater than 2 mcg/kg/min, the relationship of INR between warfarin alone to the INR on warfarin plus argatroban injection is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of argatroban injection to a dose of 2 mcg/kg/min. Repeat the INR on argatroban injection and warfarin 4 to 6 hours after reduction of the argatroban injection dose and follow the process outlined above for administering argatroban injection at doses up to 2 mcg/kg/min.

3 DOSAGE FORMS AND STRENGTHS

Intravenous Injection: 250 mg per 2.5 mL (100 mg per mL) in a single dose vial.

4 CONTRAINDICATIONS

Argatroban is contraindicated in:

Patients with major bleeding [see Warnings and Precautions (5.1)].

Patients with a history of hypersensitivity to argatroban, airway, skin, and generalized hypersensitivity reactions have been reported [see Adverse Reactions (6.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hemorrhage

Hemorrhage can occur at any site in the body in patients receiving argatroban. Unexplained fall in hematocrit or blood pressure may indicate hemorrhage. Intracranial and retroperitoneal hemorrhage have been reported [see Adverse Reactions (6.2 and 6.3)].

The risk of hemorrhage with argatroban may be increased in severe hyper tension, immediately following lumbar puncture, spinal, epidural, or intrathecal anesthesia, major surgery (especially involving the brain, spinal cord, or eye), hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders, and gastrointestinal lesions such as ulcers.

Concomitant use of argatroban with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding.

5.2 Use in Hepatic Impairment

When administering argatroban to patients with hepatic impairment, start with a lower dose and carefully titrate until the desired level of anticoagulation is achieved. Achievement of steady-state aPTT levels may take longer and require more argatroban dose adjustments in patients with hepatic impairment compared to patients with normal hepatic function [see Use in Specific Populations (8.4)].

5.3 Laboratory Tests

Anticoagulation effects associated with argatroban infusion at doses up to 40 mcg/kg/min correlate with increases of the activated partial thromboplastin time (aPTT). Although other global clot-based tests including prothrombin time (PT), the International Normalized Ratio (INR), and thrombin time (TT) have been validated by argatroban, the therapeutic ranges for these tests have not been identified for argatroban therapy. In clinical trials in PCI, the activated clotting time (ACT) was used for monitoring argatroban anticoagulant activity during the procedure. The concurrent use of argatroban and warfarin results in prolongation of the PT and INR but not the ACT in patients with warfarin alone [see Dosage and Administration (2.3) and Clinical Pharmacology (12.4)].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
6.1 Adverse Events in Patients with HIT (with or without Thrombosis)

The following safety information is based on all 568 patients treated with argatroban in Study 1 and Study 2. The safety profile of the patients from these studies is compared with that of 193 historical controls in which the adverse events were collected retrospectively. Adverse events are separated into hemorrhagic and non-hemorrhagic events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease greater than or equal to 2 g/dL that led to a transfusion of greater than or equal to 2 units, or that was intraarticular or retroperitoneal, or into a major prostatic joint. Minor bleeding was defined as bleeding that did not meet the criteria for major bleeding.

Table 5 gives an overview of the most frequently observed hemorrhagic events, presented separately by major and minor bleeding, sorted by decreasing occurrence among argatroban-treated patients with HIT (with or without thrombosis).

### Table 5

<table>
<thead>
<tr>
<th>Major Hemorrhagic Events*</th>
<th>Argatroban-Treated Patients (Study 1 and Study 2) (n = 568) %</th>
<th>Historical Control (n = 193) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall bleeding</td>
<td>5.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Genitourinary and hematuria</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Decrease in hemoglobin and hematocrit</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Multisystem hemorrhage and DIC</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Limb and BKA stump</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Minor Hemorrhagic Events*:
- Gastrointestinal: 14.4%
- Genitourinary and hematuria: 11.6%
- Decrease in hemoglobin and hematocrit: 10.4%
- Gout: 5.4%
- Hemorrhage: 2.9%
- Bruise: 2.4%

* with or without thrombosis

The following adverse reaction is also discussed in other sections of the labeling: Risk of Hemorrhage (see Warnings and Precautions (5.3)).

6.2 Adverse Events in Patients with or at Risk for HIT Patients Undergoing PCI

The following safety information is based on 91 patients initially treated with argatroban and 21 patients subsequently re-exposed to argatroban for a total of 112 PCI’s with argatroban anticoagulation. Adverse events are separated into hemorrhagic (Table 7) and non-hemorrhagic (Table 8) events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease greater than or equal to 5 g/dL that led to a transfusion of greater than or equal to 2 units, or that was intracranial, retroperitoneal, or into a major prostatic joint. The rate of major bleeding events in patients treated with argatroban in the PCI trials was 1.8%.

### Table 6

<table>
<thead>
<tr>
<th>Non-hemorrhagic Adverse Events in Patients with HIT*</th>
<th>Argatroban-Treated Patients (Study 1 and Study 2) (n = 568)</th>
<th>Historical Control (n = 193) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>8.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Fever</td>
<td>6.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>4.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Pain</td>
<td>4.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Infection</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Coughing</td>
<td>2.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>2.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Cerebrovascular disorder</td>
<td>2.3</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* Patients may have experienced more than 1 adverse event.

### Table 7

<table>
<thead>
<tr>
<th>Major Hemorrhagic Events*</th>
<th>Argatroban-Treated Patients (n = 112) %</th>
<th>Historical Control (n = 112) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retropertoneal hernormage</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Minor Hemorrhagic Events*:
- Grin (bleeding or hemorrh) 3.6%
- Gastrointestinal (includes hematemesis) 2.6%
- Genitourinary (includes hematuria) 1.8%
- Decrease in hemoglobin and/or hematocrit 1.8%
- CABG (coronary arteries) 1.8%
- Access site 0.9%
- Hemorrhage 0.9%
- Other 0.9%

* Patients may have experienced more than 1 adverse event.

6.3 Intracranial Bleeding in Other Populations

Increased risks for intracranial bleeding have been observed in investigational studies of argatroban for other uses. In a study of patients with acute myocardial infarction receiving both argatroban and thrombolytic therapy (streptokinase or tissue plasminogen activator), the overall frequency of intracranial bleeding was 16% (8 out of 510 patients). Intracranial bleeding was not observed in 317 subjects or patients who did not receive concomitant thrombolysis (see Drug Interactions (7.4)). The safety and effectiveness of argatroban for cardiac indications other than PCI in patients with HIT have not been established. Intracranial bleeding was also observed in a prospective, placebo-controlled study of argatroban in patients who had onset of acute stroke within 12 hours of study entry. Symptomatic intracranial hemorrhage
was reported in 5 of 117 patients (4.3%) who received argatroban at 1 to 3 mcg/kg/min and in none of the 54 patients who received placebo. Asymptomatic intracranial hemorrhage occurred in 5 (4.3%) and 2 (3.7%) of the patients, respectively.

6.4 Allergic Reactions
One hundred fifty-six allergic reactions or suspected allergic reactions were observed in 1,127 individuals who were treated with argatroban in clinical pharmacology studies or for various clinical indications. About 95% (1,484/1,566) of these reactions occurred in patients who concomitantly received thrombolytic therapy (e.g., streptokinase) or contrast media.

Allergic reactions or suspected allergic reactions in populations other than patients with HIT (with or without thrombosis) include (in descending order of frequency):

- Airway reactions (coughing, dyspnea): 10% or more
- Skin reactions (flush, bullous eruption): 1 to less than 10%
- General reactions (vasodilation): 1 to 10%

Limited data are available on the potential formation of drug-related antibodies. Plasma from 12 healthy volunteers treated with argatroban over 6 days showed no evidence of neutralizing antibodies. No loss of anticoagulant activity was noted with repeated administration of argatroban to more than 40 patients.

7 DRUG INTERACTIONS

7.1 Heparin
If argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin’s effect on the aPTT to decrease prior to initiation of argatroban therapy.

7.2 Oral Anticoagulant Agents
Pharmacokinetic drug-drug interactions between argatroban and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin (0.5 to 7.5 mg initial oral dose, followed by 2.5 to 6 mg/day orally for 6 to 10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) [see Dosage and Administration (2.9) and Clinical Pharmacology (12.2)].

7.3 Aspirin/Acetaminophen
No drug-drug interactions have been demonstrated between argatroban and concomitantly administered aspirin or acetaminophen [see Clinical Pharmacology (12.9)].

7.4 Thrombolytic Agents
The safety and effectiveness of argatroban with thrombolytic agents have not been established [see Adverse Reactions (6.3)].

7.5 Glycoprotein IIb/IIIa Antagonists
The safety and effectiveness of argatroban with glycoprotein IIb/IIIa antagonists have not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies of argatroban use in pregnant women. Developmental studies performed in rats (during gestation Days 7 to 17) with argatroban at intravenous doses up to 27 mg/kg/day (0.3 times the maximum recommended human dose, based on body surface area) and in rabbits (during gestation Days 6 to 18) at intravenous doses up to 10.8 mg/kg/day (0.2 times the maximum recommended human dose, based on body surface area) have revealed no evidence of harm to the fetus. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is not known whether argatroban is excreted in human milk. Argatroban is detected in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of argatroban, including the appropriate anticoagulation goals and duration of therapy, have not been established among pediatric patients. Argatroban was studied among 18 seriously ill pediatric patients who required an alternative to heparin anticoagulation. Most patients were diagnosed with HIT or suspected HIT. Age ranges of patients were less than 6 months, n = 8; six months to less than 8 years, n = 6; 8 to 16 years, n = 4. All patients had serious underlying conditions and were receiving multiple concomitant medications. Thirteen patients received argatroban solely as a continuous infusion (no bolus dose). Dosing was titrated as needed to achieve and maintain an aPTT of 1.5 to 3 times the baseline value. Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range. During the 30-day study period, thrombotic events occurred during argatroban administration to two patients and following argatroban discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial hemorrhage after 4 days of argatroban therapy in the setting of sepsis and thrombocytopenia. Another patient completed 14 days of argatroban treatment in the study, but experienced an intracranial hemorrhage while receiving argatroban following completion of the study treatment period.

When argatroban is used among seriously ill pediatric patients with HIT/HITTs who require an alternative to heparin and who have normal hepatic function, initiate a continuous infusion of argatroban at a dose of 0.75 mcg/kg/min. Initiate the infusion at a dose of 0.2 mcg/kg/min among seriously ill pediatric patients with impaired hepatic function [see Clinical Pharmacology (12.3)]. Check the aPTT two hours after the initiation of the argatroban infusion and adjust the dose to achieve the target aPTT. Increments of 0.1 to 0.25 mcg/kg/min for pediatric patients with normal hepatic function and increments of 0.05 mcg/kg/min or lower for pediatric patients with impaired hepatic function may be considered but dose selection must take into account multiple factors including the current argatroban dose, the current aPTT, target aPTT, and the clinical status of the patient. These dose recommendations are based upon a goal of aPTT prolongation of 1.5 to 3 times the baseline value and avoidance of an aPTT greater than 100 seconds.

8.5 Geriatric Use

Of the total number of subjects (1,140) in clinical studies of argatroban, 35% were 65 and over. In the clinical studies of adult patients with
The molecular formula of argatroban is C_{23}H_{36}N_{6}O_{5}S•H_{2}O. Its molecular weight is 528.66 g/mol. The structural formula is:

\[ \text{R} \]

Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate, and ether.

Argatroban injection is a sterile, colorless to pale yellow, slightly viscous solution in a single dose amber vial containing 250 mg per 2.5 mL of sterile, nonpyrogenic solution. It is supplied as a 1:10 dilution prior to intravenous use. Each mL of sterile, nonpyrogenic solution contains 100 mg argatroban and 964 mg propylene glycol.

11 CLINICAL PHARMACOLOGY

11.2 Mechanism of Action

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombin activity. Argatroban exerts its anti-coagulant effect by inhibiting thrombin-catalyzed or -induced reactions, including fibrin formation, acceleration of coagulation factors V, VII, and XIII, activation of protein C, and platelet aggregation.

Argatroban inhibits thrombin with an inhibitory constant (K_i) of 0.04 µM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

11.2.1 Pharmacodynamics

When argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow predictable, temporal response profiles, with low intersubject variability. Immediately upon initiation of argatroban infusion, anticoagulant effects are typically attained within 1 to 3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 mcg/kg/min in healthy subjects) and are linearly related to steady-state anticoagulant effects. For infusion doses up to 40 mcg/kg/min, argatroban increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT) and the thrombin time (TT) in healthy volunteers and cardiac patients. Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for argatroban infusion doses up to 10 mcg/kg/min (see Figure 1).

![Figure 1](image1)

**Relationship at Steady-State Between Argatroban Dose, Plasma Argatroban Concentration and Anticoagulant Effect**

Effect on International Normalized Ratio (INR)

Because argatroban is a direct thrombin inhibitor, co-administration of argatroban and warfarin produces a combined effect on the laboratory measurements used to monitor the INR. However, continued monitoring compared to warfarin monotherapy, exerts no additional effect on vitamin K-dependent factor activity.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. Data for 2 commonly utilized thromboplastins with ISI values of 0.68 (Ivy Diad) and 1.78 (Thrombin C Plus, Dade) are presented in Figure 2 for an argatroban dose of 2 mcg/kg higher than INR shown in Figure 2 on combined therapy of warfarin and argatroban. These data are based on results obtained in normal individuals [see Drug Interactions (7.2), Dosage and Administration (2.5)].

![Figure 2](image2)

**Figure 2**

**INR Relationship of Argatroban Plus Warfarin Versus Warfarin Alone**

Figure 2 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban at a dose of 2 mcg/kg/min. To calculate INR for warfarin alone (INRw), based on INR for co-therapy of warfarin and argatroban (INRwA), when the argatroban dose is 2 mcg/kg/min, use the equation next to the appropriate curve. Example: At a dose of 2 mcg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INRW) = INRW would allow a prediction of the INR on warfarin alone (INRW).

Thus, using an INRW value of 4 obtained on combined therapy, INRW = 0.19 + 0.57 (4) = 2.47 as the value for INR on warfarin alone. The error (confidence interval), associated with a prediction is ± 0.4. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Furthermore, for argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INRW from INRW is ≤ 1. Thus, INRW cannot be reliably predicted from INRW at doses greater than 2 mcg/kg/min.

12.3 Pharmacokinetics

**Distribution**

Argatroban distributes mainly in the extra cellular fluid as evidenced by an apparent steady-state volume of distribution of 174 mL/kg (12.18 L in a 70 kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α-acid glycoprotein being 20% and 34%, respectively.

**Metabolism**

The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methylthreohydrongluquine ring in the liver. The formation of each of the 4 known metabolites is catalyzed by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than argatroban. Unchanged argatroban is the major component in plasma. The plasma concentrations of M1 range between 2% and 20% of that of the parent compound. M2 to M4 are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of an effect of erythromycin (a potent CYP2C9/K inhibitor) on argatroban pharmacokinetics, suggest that CYP3A4/5-mediated metabolism is not an important elimination pathway in vivo.

Total body clearance is approximately 5.1 mL/min (0.31 L/hr) for infusion doses up to 40 mcg/kg/min. The terminal elimination half-life of argatroban is between 39.51 minutes and 12.2 hours.

There is no interconversion of the 21- (R)-21- (S) diastereoisomers.

**Excretion**

Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which 14C-argatroban (5 mcg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity lost subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

**Special Populations**

**Hepatic Impairment**

The dosages of argatroban should be decreased in patients with hepatic impairment (see Dosage and Administration (2.3) and Warnings and Precautions (5.2)). Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 mcg/kg/min, hepatic impairment is associated with increased clearance and increased elimination half-life of argatroban (to 1.9 mL/kg/min and 181 minutes, respectively, for patients with a Child-Pugh score greater than 6).

**Renal Impairment**

No dosage adjustment is necessary in patients with renal dysfunction.

The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean ClCr = 95 ± 16 mL/min) and in 18 subjects with mild (mean ClCr = 64 ± 10 mL/min), moderate (mean ClCr = 41 ± 5.8 mL/min), and severe (mean ClCr = 25 ± 7 mL/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at doses up to 5 mcg/kg/min were not significantly affected by renal dysfunction.

**Storage**

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[5-[[((2S,5R)-1-acid glycoprotein being 20% and 34%, respectively.

The plasma ratio of these diastereoisomers is unchanged by metabolism of argatroban at dosages up to 5 mcg/kg/min. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Thus, for argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INRW from INRW is ≤ 1. Thus, INRW cannot be reliably predicted from INRW at doses greater than 2 mcg/kg/min.

**Dosage and Administration**

When argatroban is administered as a continuous infusion of 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, argatroban dose. In clinical studies, anticoagulation parameters generally returned to baseline levels within 2 to 4 hours after discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment.

No specific antidote to argatroban is available; if life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, discontinuation argatroban is recommended and measurements of aPTT and other anticoagulation parameters are performed. When argatroban was administered as a continuous infusion (2 mcg/kg/min) prior to and during a 4-hour hemodialysis session, approximately 20% of argatroban was cleared through dialysis.

Single intravenous doses of argatroban at 200, 124, 150, and 200 mcg/kg were lethal to mice, rats, rabbits, and dogs, respectively. The systemic toxicities were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs, and coma.

11 DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor and the chemical name is 1-[5-[[((2S,5R)-1-acid glycoprotein being 20% and 34%, respectively.

The plasma ratio of these diastereoisomers is unchanged by metabolism of argatroban at dosages up to 5 mcg/kg/min. Similar linear relationships and prediction errors exist for argatroban at a dose of 1 mcg/kg/min. Thus, for argatroban doses greater than 2 mcg/kg/min, the error associated with predicting INRW from INRW is ≤ 1. Thus, INRW cannot be reliably predicted from INRW at doses greater than 2 mcg/kg/min.
Use of argatroban was evaluated in a study of 12 patients with stable end-stage renal disease undergoing chronic intermittent hemodi-
ysis. Argatroban was administered at a rate of 2 to 3 mcg/kg/min (beginning at 4 hours prior to dialysis) or as a bolus dose of 250 mcg/kg at the start of dialysis followed by a continuous infusion of 2 mcg/kg/min. Although these regimens did not achieve the goal of main-
aining ACT values at 1.8 times the baseline value throughout most of the hemodialysis period, the hemodialysis sessions were successfully completed with both of these regimens. The mean ACTs produced in this study ranged from 1.39 to 1.82 times baseline and the mean aPTTs ranged 1.96 to 3.4 times baseline. When argatroban was administered as a continuous infusion of 2 mcg/kg/min prior to and during a 4-hour hemodialysis session, approximately 20% was cleared through dialysis.

Ace: General
There are no clinically significant effects of age or gender on the pharma-
ocokinetics or pharmacodynamics (e.g., aPTT) of argatroban in adults. Pediat-
ic:
Argatroban clearance is decreased in seriously ill pediatric patients. Pha-
macokinetic parameters of argatroban were characterized in a popu-
lation pharmacokinetic/pharmacodynamic analysis with sparse data in some seriously ill pediatric patients. Clearance in pediatric pat-
ients (0.16 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Pediatric patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to pediatric patients with normal bilirubin levels [see Use In Specific Populations (8.4)].

Drug-Drug Interactions:
Dialysis:
In 12 healthy volunteers, intravenous infusion of argatroban (2 mcg/kg/min) over 5 days (study days 11 to 15) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).

10.5
Enzyme induction:
In 10 healthy subjects, orally administered enzytoxyn (a potent inhibitor of CYP3A4/5) at 500 mg four times daily for 7 days had no effect on the pharmacokinetics of argatroban at a dose of 1 mcg/kg/min over 6 hours. These data suggest oxidative metabolism by CYP3A4 is not an important elimination pathway in vivo for argatroban.

Aspirin and Acetylsalicylic Acid:
Drug-drug interactions have not been demonstrated between argatro-
ban and aspirin (50 mg orally every 6 hours). In a population pharmacoki-
tics study, argatroban was given intravenously at 5 mcg/kg/min to patients with atrial fibrillation and receiving concomitant aspirin (150 mg orally). The steady-state plasma concentration of aspirin was not different from that observed in patients who received aspirin alone.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies with argatroban have not been performed.

14. CLINICAL STUDIES
14.1 Heparin-Induced Thrombocytopenia
The safety and efficacy of argatroban were evaluated in a historically controlled, dose-finding and safety study (Study 1) and a follow-on efficacy and safety study (Study 2). These studies were comparable with regard to study design, study objectives, dosing regimens as well as study outcome, conduct, and monitoring. In these studies, 568 adult patients were treated with argatroban and 193 adult patients made up the historical control group. Patients had a clinical diagnosis of heparin-induced thrombocytopenia, either without thrombosis (HIT) or with thrombosis (HITTS [heparin-induced thrombocytopenia and thrombosis syndrome]) and were males or non-pregnant females between the ages of 18 and 80 years old. HITTS was defined by a fall in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation. In Study 1, all patients with HITTS also had an arterial or venous thrombosis documented by appropriate imaging techniques or supported by clinical evidence such as acute myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascu-
lar occlusion. Patients who had documented histories of positive heparin-dependent antiboody tests without current thrombocytopenia or heparin challenge (e.g., patients with latent disease) were also included if they required anticoagulation.

These studies did not include patients with documented unexplained aPTTs or platelet counts at baseline, documented coagulation disorder or bleeding diathesis unrelated to HIT, a lumbar puncture within the past 7 days or a history of previous aneurysm, hemorrhage, or a thrombotic stroke within the past 6 months unrelated to HIT.

The initial dose of argatroban was 2 mcg/kg/min. Two hours after the start of the argatroban infusion, an aPTT level was obtained and dose adjustments were made (up to a maximum of 10 mcg/kg/min) to achieve a steady-state aPTT value that was 1.5 to 3 times the baseline value, not to exceed 100 seconds. The mean aPTT level for HIT and HITTS patients during the argatroban infusion increased from baseline values of 34 and 38 seconds, respectively, to 62.5 and 64.5 seconds, respectively.

The primary efficacy analysis was based on a comparison of event rates for a composite endpoint that included death (all causes), amputa-
tion (all causes) or new thrombosis during the treatment and follow-up period (study days 0 to 37). Secondary analyses included evaluation of the event rates for the components of the composite endpoint as well as time-to-event analyses.

In Study 1, a total of 304 patients were enrolled as follows: active HIT (n = 129), active HITTS (n = 144), or latent disease (n = 31). Among the HIT patients, 139 (72%) had active HIT, 46 (24%) had active HITTS, and 8 (4%) had latent disease. Among the HITTS patients, those with active HIT and those with latent disease were ana-
yzed together. Positive laboratory confirmation of HIT/HITTS by the heparin-induced platelet aggregation test or serotonin release assay was demonstrated in 174 of 304 (57%) argatroban-treated patients (i.e., in 80 with HIT or latent disease and 94 with HITTS) and in 149 of 193 (77%) historical controls (i.e., in 119 with HIT or latent disease and 30 with HITTS). The results for the remainder of the patients and controls were either negative or not determined.

There was a significant improvement in the composite outcome in patients with HIT or HITTS treated with argatroban versus those in the historical control group (see Table 10). The components of the composite endpoint are shown in Table 10.

Table 10: Efficacy Results of Study 1: Composite Endpoint and Individual Components, Ranked by p Value

<table>
<thead>
<tr>
<th>Component</th>
<th>Control</th>
<th>Argatroban</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>42 (21.0)</td>
<td>27 (14.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Amputation</td>
<td>3 (1.5)</td>
<td>2 (1.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>New</td>
<td>22 (11.6)</td>
<td>11 (5.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Death (all causes), amputation (all causes), or new thrombosis within 37-day study period.

Reprinted as the most severe outcome among the components of the composite endpoint (severity ranking: death > amputation > new thrombosis), patients may have had multiple outcomes.

14.2 Percutaneous Coronary Intervention (PCI) Patients with or at Risk for HIT

In Study 2, a total of 264 patients were enrolled as follows: HIT (n = 125) or HITTS (n = 139). There was a significant improvement in the composite efficacy outcome for argatroban-treated patients, versus the same historical control group from Study 1, among patients having HIT (25.6% vs. 38.8%), patients required HITTS (42% vs. 56.5%), and patients having either HIT or HITTS (33.7% vs. 43%). Time-to-
event analyses showed a significant improvement in time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban by these analyses.

The time-to-event analysis for the composite endpoint is shown in Figure 3 for patients with HIT and Figure 4 for patients with HITTS.

Figure 3: Time-to-First Event for the Composite Efficacy Endpoint: HIT Patients

<table>
<thead>
<tr>
<th>Efficacy Result</th>
<th>Control</th>
<th>Argatroban</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
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<td>Death</td>
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<td>22 (11.6)</td>
<td>11 (5.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Censored indicates no clinical endpoint (defined as death, amputa-
tion, or new thrombosis) was observed during the follow-up period (maximum period of follow-up was 37 days).

In Study 2, a total of 264 patients were enrolled as follows: HIT (n = 125) or HITTS (n = 139). There was a significant improvement in the composite efficacy outcome for argatroban-treated patients, versus the same historical control group from Study 1, among patients having HIT (25.6% vs. 38.8%), patients required HITTS (42% vs. 56.5%), and patients having either HIT or HITTS (33.7% vs. 43%). Time-to-
event analyses showed a significant improvement in time-to-first event in patients with HIT or HITTS treated with argatroban versus those in the historical control group. The between-group differences in the proportion of patients who remained free of death, amputation, or new thrombosis were statistically significant in favor of argatroban.

Anticoagulant Effect:
In Study 1, the mean (± SE) dose of argatroban administered was 2.0 ± 0.1 mcg/kg/min in the HIT arm and 1.9 ± 0.1 mcg/kg/min in the HITTS arm. During the 12-hour period, patients with HITTS achieved a target aPTT at least 1.5-fold greater than the baseline aPTT at the first assessment occurring on average at 4.6 hours (HIT) and 3.9 hours (HITTS) following initiation of argatroban therapy.

No enhancement of aPTT response was observed in subjects receiv-
ing repeated administration of argatroban.

Platelet Count Recovery
In Study 1, 50% of patients with HIT and 58% of patients with HITTS, had a recovery of platelet count by Day 3. Platelet Count Recovery was defined as an increase in platelet count to greater than 100,000/μL or to at least 1.5-fold greater than the baseline platelet count (platelet count at study initiation) by Day 3 of the study.

14.4 Pericoronary Coronary Intervention (PCI) Patients with or at Risk for HIT

In a similar designed trials, argatroban was administered to 91 patients with current or previous clinical diagnosis of HIT or heparin-
dependent antibodies, who underwent a total of 112 pericoronary
coronary interventions (PCIs) including percutaneous transluminal coronary angioplasty (PTCA), coronary stent placement, or atherectomy. Among the 91 patients undergoing their first PCI with argatroban, notable ongoing or recent medical history included myocardial infarction (n = 35), unstable angina (n = 29), and chronic angina (n = 34). There were 33 females and 58 males. The average age was 67.6 years (median 70.7, range 44 to 86), and the average weight was 82.5 kg (median 81 kg, range 49 to 141).

Twenty-one of the 91 patients had a repeat PCI using argatroban an average of 150 days after their initial PCI. Seven of 91 patients received glycoprotein IIb/IIIa inhibitors. Safety and efficacy were assessed against historical control populations who had been anticoagulated with heparin.

All patients received oral aspirin (325 mg) 2 to 24 hours prior to the interventional procedure. After venous or arterial sheaths were in place, anticoagulation was initiated with a bolus of argatroban of 350 mcg/kg via a large-bore intravenous line or through the venous sheath over 3 to 5 minutes. Simultaneously, a maintenance infusion of 25 mcg/kg/min was initiated to achieve a therapeutic activated clotting time (ACT) of 300 to 450 seconds. If necessary to achieve this therapeutic range, the maintenance infusion dose was titrated (15 to 40 mcg/kg/min) and/or an additional bolus dose of 150 mcg/kg could be given. Each patient’s ACT was checked 5 to 10 minutes following the bolus dose. The ACT was checked as clinically indicated. Arterial and venous sheaths were removed no sooner than 2 hours after discontinuation of argatroban and when the ACT was less than 160 seconds.

If a patient required anticoagulation after the procedure, argatroban could be continued, but at a lower infusion dose between 2.5 and 5 mcg/kg/min. An aPTT was drawn 2 hours after this dose reduction and the dose of argatroban was then adjusted as clinically indicated (not to exceed 10 mcg/kg/min), to reach an aPTT between 1.5 and 3 times baseline value (not to exceed 100 seconds).

In 82 of the 112 interventions (82%), the patient received the initial bolus of 350 mcg/kg and an initial infusion dose of 25 mcg/kg/min. The majority of patients did not require additional bolus doses during the PCI procedure. The mean value for the initial ACT measurement after the start of dosing for all interventions was 379 sec (median 338 sec; 5th percentile-95th percentile 238 to 675 sec). The mean ACT value per intervention over all measurements taken during the procedure was 416 sec (median 390 sec; 5th percentile-95th percentile 261 to 698 sec). About 65% of patients had ACTs within the recommended range of 300 to 450 seconds throughout the procedure. The investigators did not achieve anticoagulation within the recommended range in about 23% of patients. However, in this small sample, patients with ACTs below 300 seconds did not have more coronary thrombotic events, and patients with ACTs over 450 seconds did not have higher bleeding rates.

Acute procedural success was defined as lack of death, emergent coronary artery bypass graft (CABG), or Q-wave myocardial infarction. Acute procedural success was reported in 98.2% of patients who underwent PCIs with argatroban anticoagulation compared with 94.3% of historical control patients anticoagulated with heparin (p = NS). Among the 112 interventions, 2 patients had emergency CABGs. 3 had repeat PCIs, 4 had non-Q-wave myocardial infarctions, 3 had myocardial ischemia, 1 had an abrupt closure, and 1 had an impending closure (some patients may have experienced more than 1 event). No patients died.

16 HOW SUPPLIED/STORAGE AND HANDLING
NDC 63323-226-03, 250 mg per 2.5 mL (100 mg per mL) single dose vial, packaged individually.

Storage
Store the vial in original carton at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from freezing. Protect from light (keep in outer carton). If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

The container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION
Inform patients of the risks associated with Argatroban Injection as well as the plan for regular monitoring during administration of the drug.

Specifically, inform patients to report:
- the use of any other products known to affect bleeding;
- any medical history that may increase the risk for bleeding, including a history of severe hypertension; recent lumbar puncture or spinal anesthesia; major surgery, especially involving the brain, spinal cord, or eye; hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations;
- any bleeding signs or symptoms;
- the occurrence of any signs or symptoms of allergic reactions (e.g., airway reactions, skin reactions and vasodilatation reactions).

Manufactured by:

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