Ordering Summary

Aggrastat Injection Premixed is a clear, non-preserved, sterile solution pre-mixed in a vehicle made iso-osmotic with 0.9% sodium chloride.

Manufacturer stability is 36 months. Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F). Do not freeze. Aggrastat is provided in a foil overpouch (pre-mixed bags) or carton (bolus vial) for protection from light during storage.

<table>
<thead>
<tr>
<th>Product</th>
<th>NDC Number</th>
<th>How Supplied</th>
<th>Dimensions</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mL Bolus Vial</td>
<td>25208-001-04</td>
<td>3.75 mg in 15 mL (250 mcg/mL) pre-mixed vial</td>
<td>2.6” H x 1.7” W x 1.6” D (contains 1 ready-to-use vial)</td>
<td>0.66 lbs</td>
</tr>
<tr>
<td>100 mL Bag</td>
<td>25208-002-01</td>
<td>5 mg in 100 mL (50 mcg/mL) pre-mixed bag</td>
<td>11.8” H x 5.8” W x 1.1” D (contains 1 ready-to-use bag)</td>
<td>0.2 lbs</td>
</tr>
<tr>
<td>250 mL Bag</td>
<td>25208-002-02</td>
<td>12.5 mg in 250 mL (50 mcg/mL) pre-mixed bag</td>
<td>12.8” H x 6.3” W x 1.7” D (contains 1 ready-to-use bag)</td>
<td>0.9 lbs</td>
</tr>
</tbody>
</table>

Aggrastat is contracted with all national GPOs. Please contact one of our product specialists for contract pricing. (1-800-509-0544: option 5, or aggrastat@medicure.com).

Aggrastat is available through normal distribution at your wholesaler. See reverse for wholesaler item numbers. For immediate supply, Aggrastat is available as a drop shipment via Express Overnight Delivery. It is important to provide your wholesaler with updated demand forecasts for Aggrastat.

If you require any assistance working with your wholesaler, or need supply immediately, please contact our ordering department (1-800-509-0544: option 1, or ordering@medicure.com).
## Wholesaler Availability

<table>
<thead>
<tr>
<th>Wholesaler</th>
<th>3.75 mg/15 mL Bolus Vial</th>
<th>5 mg/100 mL Pre-mixed Bag</th>
<th>12.5 mg/250 mL Pre-mixed Bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmerisourceBergen Drug Corporation</td>
<td>10169784</td>
<td>10043979</td>
<td>10040778</td>
</tr>
<tr>
<td>Cardinal Health, Inc.</td>
<td>5293881</td>
<td>4073318</td>
<td>4073334</td>
</tr>
<tr>
<td>HD Smith Wholesale Drug Company</td>
<td>5617626</td>
<td>1499250</td>
<td>1092345</td>
</tr>
<tr>
<td>McKesson Corporation</td>
<td>3590874</td>
<td>1468677</td>
<td>1480433</td>
</tr>
<tr>
<td>Morris &amp; Dickson Company, LLC</td>
<td>856963</td>
<td>930917</td>
<td>859645</td>
</tr>
</tbody>
</table>

### Authorized Distributors of Record for Aggrastat are listed below:

- AmerisourceBergen Drug Corporation
- Borschow Hospital & Medical Supplies
- Cardinal Health, Inc.
- Cesar Castillo, Inc.
- Dakota Drug, Inc.
- DMS Pharmaceutical Group, Inc.
- HD Smith Wholesale Drug Company
- McKesson Corporation
- Morris & Dickson Company, LLC
- Smith Drug Company

### Contact a Product Specialist: 1-800-509-0544 (#5)

**www.aggrastatHDB.com**

### IMPORTANT SAFETY INFORMATION

**Indication:** Aggrastat is indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS).

**Contraindications:** Known hypersensitivity to any component of Aggrastat; history of thrombocytopenia with prior exposure to Aggrastat; active internal bleeding, or history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month.

**Warnings and Precautions:** Aggrastat can cause serious bleeding. If bleeding cannot be controlled discontinue Aggrastat; thrombocytopenia: discontinue Aggrastat and heparin.

**Adverse Reactions:** Bleeding is the most commonly reported adverse reaction.
AGGRASTAT® (tirofiban hydrochloride) injection, for intravenous use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

AGGRASTAT® is a platelet aggregation inhibitor indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS). (1)

DOSAGE AND ADMINISTRATION

• Administer intravenously 25 mcg/kg within 5 minutes and then 0.15 mcg/kg/min for up to 18 hours. In patients with creatinine clearance ≤60 mL/min, give 25 mcg/kg within 5 minutes and then 0.075 mcg/kg/min. (2)

DOSAGE FORMS AND STRENGTHS

• Injection: 5 mg/100mL (50 mcg/mL) in 100 mL bag
• Injection: 12.5 mg/250mL (50 mcg/mL) in 250 mL bag
• Injection: 5 mg/100mL (50 mcg/mL) in 100 mL vial
• Injection: 3.75 mg/15mL (250 mcg/mL) in 15 mL bolus vial

CONTRAINDICATIONS

• Known hypersensitivity to any component of AGGRASTAT. (4)
• History of thrombocytopenia with prior exposure to AGGRASTAT. (4)
• Active internal bleeding, or history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month. (4)

WARNINGS AND PRECAUTIONS

• AGGRASTAT can cause serious bleeding. If bleeding cannot be controlled discontinue AGGRASTAT. (5.1)
• Thrombocytopenia: Discontinue AGGRASTAT and heparin. (5.2)

ADVERSE REACTIONS

Bleeding is the most commonly reported adverse reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Medicure at 1-800-509-0544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Coadministration of fibrinolytics, anticoagulants and antiplatelet agents, increases the risk of bleeding. (7)

USE IN SPECIFIC POPULATIONS

• Renal Insufficiency: Reduce the dose in patients with severe renal insufficiency. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2016
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
AGGRASTAT is indicated to reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction, or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTEMI).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
The recommended dosage is 25 mcg/kg administered intravenously within 5 minutes and then 0.15 mcg/kg/min for up to 18 hours.

2.2 Administration
For intravenous use only. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To open the INTRAVIA bag, first tear off its foil overpouch. The plastic may be somewhat opaque because of moisture absorption during sterilization; the opacity will diminish gradually. Check for leaks by squeezing the inner bag firmly; if any leaks are found or sterility is suspect then the solution should be discarded. Do not use unless the solution is clear and the seal is intact.

Administration Instructions:
1. Withdraw the bolus dose of AGGRASTAT from the 15 mL premixed bolus vial into a syringe. Alternatively, the bolus dose of AGGRASTAT may be administered from the 100 mL premixed vial or from the premixed bags. Do not dilute. Administer the bolus dose within 5 minutes via a syringe or IV pump.
2. Immediately following the bolus dose administration, administer the maintenance infusion from the 100 mL premixed vial or bags via an IV pump.
3. Discard any unused portion left in the vial or bag.

The recommended bolus volume using the 15 mL premixed bolus vial can be calculated using the following equation:

$$\text{Bolus Volume (mL)} = \frac{25 \text{ mcg/kg} \times \text{ body weight (kg)}}{250 \text{ mcg/mL}}$$

The recommended bolus volume using the 100 mL premixed vial or premixed bags can be calculated using the following equation:

$$\text{Bolus Volume (mL)} = \frac{25 \text{ mcg/kg} \times \text{ body weight (kg)}}{50 \text{ mcg/mL}}$$

The recommended infusion rate for patients with CrCl (Creatinine Clearance) >60 mL/min using the 100 mL premixed vial or premixed bags can be calculated using the following equation:

$$\text{Infusion Rate for CrCl>60 mL/min (mL/h)} = \frac{0.15 \text{ mcg/kg/min} \times \text{ body weight (kg)} \times 60 \text{ min/h}}{50 \text{ mcg/mL}}$$

Example calculation of infusion rate for 60 kg patient with CrCl >60 mL/min using the 100 mL premixed vial or premixed bags:

$$\text{Infusion Rate for CrCl>60 mL/min (mL/h)} = \frac{0.15 \text{ mcg/kg/min} \times 60 \text{ kg} \times 60 \text{ min/h}}{50 \text{ mcg/mL}} = 10.8 \text{ mL/h}$$

Drug Compatibilities
AGGRASTAT can be administered in the same intravenous line as heparin, atropine sulfate, dobutamine, dopamine, epinephrine hydrochloride (HCl), famotidine injection, furosemide, lidocaine, midazolam HCl, morphine sulfate, nitroglycerin, potassium chloride, and propranolol HCl. Do not administer AGGRASTAT through the same IV line as diazepam. Do not add other drugs or remove solution directly from the INTRAVIA bag with a syringe.

2.3 Dose Adjustment for Renal Impairment
The recommended dosage in patients with CrCl ≤60 mL/min is 25 mcg/kg intravenously within 5 minutes and then 0.075 mcg/kg/min, for up to 18 hours.

The recommended infusion rate for patients with CrCl ≤60 mL/min using the 100 mL premixed vial or premixed bags can be calculated using the following equation:

$$\text{Infusion Rate for CrCl≤60 mL/min (mL/h)} = \frac{0.075 \text{ mcg/kg/min} \times \text{ body weight (kg)} \times 60 \text{ min/h}}{50 \text{ mcg/mL}}$$

3 DOSAGE FORMS AND STRENGTHS
AGGRASTAT is a clear, non-preserved, colorless, isosmotic, sterile premixed injection with sodium chloride for tonicity adjustment available in the following presentations:

Table 1 AGGRASTAT strength and packaging

<table>
<thead>
<tr>
<th>Strength</th>
<th>Volume - Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mcg/mL</td>
<td>100 mL - bag</td>
</tr>
<tr>
<td>250 mcg/mL</td>
<td>15 mL - bolus vial</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS
AGGRASTAT is contraindicated in patients with:

- Severe hypersensitivity reaction to AGGRASTAT (i.e., anaphylactic reactions) [see Adverse Reactions (6.1)].
- A history of thrombocytopenia following prior exposure to AGGRASTAT [see Adverse Reactions (6.2)].
- Active internal bleeding or a history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month [see Adverse Reactions (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding
Bleeding is the most common complication encountered during therapy with AGGRASTAT. Most bleeding associated with AGGRASTAT occurs at the arterial access site for cardiac catheterization. Minimize the use of traumatic or potentially traumatic procedures such as arterial and venous punctures, intramuscular injections, nasotracheal intubation, etc.

Concomitant use of fibrinolytics, anticoagulants and antiplatelet drugs increases the risk of bleeding.

5.2 Thrombocytopenia
Profound thrombocytopenia has been reported with AGGRASTAT. Monitor platelet counts beginning about 6 hours after treatment initiation and daily thereafter. If the platelet count decreases to <90,000/mm³, monitor platelet counts to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, discontinue AGGRASTAT and heparin. Previous exposure to a glycoprotein (GP) IIb/IIIa receptor antagonist may increase the risk of developing thrombocytopenia [see Adverse Reactions (6.1)].
6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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 clinical practice.

In the PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management), PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management — Patients Limited by Unstable Signs and Symptoms) and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trials, 1946 patients received AGGRASTAT in combination with heparin and 2002 patients received AGGRASTAT alone for about 3 days. Forty-three percent of the population was >65 years of age and approximately 30% of patients were female. In clinical studies with the recommended regimen (25 mcg/kg bolus followed by a 0.15 mcg/kg/ min maintenance infusion), AGGRASTAT was administered in combination with aspirin, clopidogrel and heparin or bivalirudin to over 8000 patients for typically ≤24 hours. Approximately 30% of the population was >65 years of age and approximately 25% were female.

Bleeding

PRISM-PLUS Regimen

The incidences of major and minor bleeding using the TIMI criteria in the PRISM-PLUS study are shown below.

<table>
<thead>
<tr>
<th>Bleeding (TIMI Criteria)</th>
<th>AGGRASTAT + heparin (N=773)</th>
<th>Heparin alone (N=797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>1.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>10.5%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Transfusions</td>
<td>4.0%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

° 0.4 mcg/kg/min initial infusion; 0.10 mcg/kg/min maintenance infusion.
§ Major = Hemoglobin drop of <5.0 g/dL with or without an identified site, intracranial hemorrhage, or cardiac tamponade.
§ Minor = Hemoglobin drop of >3.0 g/dL with bleeding from a known site, spontaneous gross hematuria, hematemesis or hemoptysis.

The incidence rates of TIMI major bleeding in patients undergoing percutaneous procedures in PRISM-PLUS are shown below.

<table>
<thead>
<tr>
<th>AGGRASTAT + heparin</th>
<th>Heparin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Prior to Procedures</td>
<td>773</td>
</tr>
<tr>
<td>Following Angiography</td>
<td>697</td>
</tr>
<tr>
<td>Following PTCA</td>
<td>239</td>
</tr>
</tbody>
</table>

The incidence rates of TIMI major bleeding in patients undergoing coronary artery bypass graft surgery (CABG) in PRISM-PLUS within one day of discontinuation of AGGRASTAT were 17% on AGGRASTAT plus heparin (N=29) and 35% on heparin alone (N=31).

Recommended ("High-Dose Bolus") Regimen

Rates of major bleeds (including any intracranial, intraocular or retroperitoneal hemorrhage, clinically overt signs of hemorrhage associated with a drop in hemoglobin of >3 g/dL or any drop in hemoglobin by 4g/dL, bleeding requiring transfusion of ≥2U blood products, bleeding directly resulting in death within 7 days or hemodynamic compromise requiring intervention) were consistent with the rates observed in subjects administered the PRISM-PLUS regimen of AGGRASTAT. There was a trend toward greater bleeding in ST segment elevation myocardial infarction (STEMI) patients treated with fibrinolytics prior to administration of AGGRASTAT using the recommended regimen during rescue PCI.

Non-Bleeding

The incidences of non-bleeding adverse events that occurred at an incidence of >1% and numerically higher than control, regardless of drug relationship, are shown below.

Table 4 Non-bleeding Adverse Reactions in PRISM-PLUS

<table>
<thead>
<tr>
<th>Reaction</th>
<th>AGGRASTAT + heparin (N=1953) %</th>
<th>Heparin alone (N=1887) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema/swelling</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pain, pelvic</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Reaction, vasovagal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dissection, coronary artery</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain, leg</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System/Psychiatric</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Skin Appendage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Thrombocytopenia

Patients treated with AGGRASTAT plus heparin, were more likely to experience decreases in platelet counts than were those on heparin alone. These decreases were reversible upon discontinuation of AGGRASTAT. The percentage of patients with a decrease of platelets to <90,000/mm³ was 1.5%, compared with 0.6% in the patients who received heparin alone. The percentage of patients with a decrease of platelets to <50,000/mm³ was 0.3%, compared with 0.1% of the patients who received heparin alone.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of AGGRASTAT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Hypersensitivity: Severe allergic reactions including anaphylactic reactions have occurred during the first day of AGGRASTAT infusion, during initial treatment, and during readministration of AGGRASTAT. Some cases have been associated with severe thrombocytopenia (platelet counts <10,000/mm³). No information is available on the formation of antibodies to tirofiban.

7 DRUG INTERACTIONS

Comitant use of fibrinolytics, anticoagulants and antiplatelet drugs increases the risk of bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Tirofiban has been shown to cross the placenta in pregnant rats and rabbits. Studies with tirofiban HCl at intravenous doses up to 5 mg/kg/day (about 5 and 13 times the maximum recommended daily human dose for rat and rabbit, respectively, when compared on a body surface area basis) have revealed no harm to the fetus.

8.3 Nursing Mothers

It is not known whether tirofiban is excreted in human milk. However, significant levels of tirofiban were shown to be present in rat milk. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, discontinue nursing or discontinue AGGRASTAT.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.
Its molecular formula is C_{36}H_{37}N_{3}O_{5}S•HCl•H_{2}O. Tirofiban hydrochloride monohydrate is chemically described as N-(butylsulfonyl)-O-[(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate. Its molecular formula is C_{36}H_{37}N_{3}O_{5}S•HCl•H_{2}O and its structural formula is:

\[\text{HN} \quad \text{OH} \quad \text{CH}_{3} \quad \text{CH}_{2} \quad \text{CH}_{2} \quad \text{OH} \quad \text{OH} \quad \text{HCl} \quad \text{H}_{2} \text{O} \]

Tirofiban hydrochloride monohydrate is a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 495.08. It is very slightly soluble in water.

AGGRASTAT Injection Premixed is supplied as a sterile solution in water for injection, for intravenous use. The pH of the solution ranges from 5.5 to 6.5 adjusted with hydrochloric acid and/or sodium hydroxide.

Each 100 mL of the premixed, isosmotic intravenous injection contains 5.618 mg tirofiban hydrochloride monohydrate equivalent to 5 mg tirofiban (50 mcg/mL) and the following inactive ingredients: 0.9 g sodium chloride, 54 mg sodium citrate dihydrate, and 3.2 mg citric acid anhydrous.

Each 250 mL of the premixed, isosmotic intravenous injection contains 14.045 mg tirofiban hydrochloride monohydrate equivalent to 12.5 mg tirofiban (50 mcg/mL) and the following inactive ingredients: 2.25 g sodium chloride, 135 mg sodium citrate dihydrate, and 8 mg citric acid anhydrous.

AGGRASTAT Injection Premixed Bolus Vial is supplied as a sterile, isosmotically concentrated solution for intravenous bolus injection, in 15 mL vials. No dilution is required. Each 15 mL of the premixed, isosmotic intravenous injection bolus vial contains 4.215 mg of tirofiban hydrochloride monohydrate equivalent to 3.75 mg of tirofiban and the following inactive ingredients: 120 mg sodium chloride, 40.5 mg sodium citrate dihydrate, and 2.4 mg citric acid anhydrous and water for injection.

AGGRASTAT contains tirofiban hydrochloride, a non-peptide antagonist of the platelet GP IIb/IIIa receptor, which inhibits platelet aggregation.

Tirofiban hydrochloride monohydrate is chemically described as N-(butylsulfonyl)-O-[(4-piperidinyl)butyl]-L-tyrosine monohydrochloride monohydrate.

Tirofiban hydrochloride monohydrate is a white to off-white, non-hygroscopic, free-flowing powder, with a molecular weight of 495.08. It is very slightly soluble in water.

AGGRASTAT Injection Premixed is supplied as a sterile solution in water for injection, for intravenous use. The pH of the solution ranges from 5.5 to 6.5 adjusted with hydrochloric acid and/or sodium hydroxide.

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AGGRASTAT Injection Premixed Bolus Vial is supplied as a sterile, isosmotically concentrated solution for intravenous bolus injection, in 15 mL vials. No dilution is required. Each 15 mL of the premixed, isosmotic intravenous injection bolus vial contains 4.215 mg of tirofiban hydrochloride monohydrate equivalent to 3.75 mg of tirofiban and the following inactive ingredients: 120 mg sodium chloride, 40.5 mg sodium citrate dihydrate, and 2.4 mg citric acid anhydrous and water for injection.
Two large-scale clinical studies established the efficacy of AGGRASTAT in the treatment of patients with NSTE-ACS (unstable angina/non-ST elevation MI). The two studies examined AGGRASTAT alone and added to heparin, prior to and after percutaneous coronary revascularization (if indicated) (PRISM-PLUS) and in comparison to heparin in a similar population (PRISM). These trials are discussed in detail below.

**PRISM-PLUS (Platelet Receptor Inhibition for Ischemic Syndrome Management — Patients Limited by Unstable Signs and Symptoms)**

In the double-blind PRISM-PLUS trial, 1570 patients with documented NSTE-ACS within 12 hours of entry into the study were randomized to AGGRASTAT (30 minute initial infusion of 0.4 mcg/kg/min followed by a maintenance infusion of 0.10 mcg/kg/min) in combination with heparin (bolus of 5,000 U followed by an infusion of 1,000 U/h titrated to maintain an APTT of approximately 2 times control) or to heparin alone. All patients received concomitant aspirin unless contraindicated. Patients who were medically managed or who underwent revascularization procedures were studied. Patients underwent 48 hours of medical stabilization on study drug therapy, and they were to undergo angiography before 96 hours (and, if indicated, angioplasty/atherectomy, while continuing on AGGRASTAT and heparin for 12-24 hours after the procedure). AGGRASTAT and heparin could be continued for up to 108 hours. Exclusions included contraindications to anticoagulation, decompensated heart failure, platelet count <150,000/mm3, and serum creatinine >2.5 mg/dL. The mean age of the population was 63 years; 32% of patients were female and approximately half of the population presented with non-ST elevation myocardial infarction. On average, patients received AGGRASTAT for 71 hours.

A third group of patients was initially randomized to AGGRASTAT alone (no heparin). This arm was stopped when the group was found, at an interim look, to have greater mortality than the other two groups.

The primary endpoint of the study was a composite of refractory ischemia, new MI and death within 7 days. There was a 32% risk reduction in the overall composite primary endpoint. The components of the composite were examined separately and the results are shown in Table 5. Note that the sum of the individual components may be greater than the composite (if a patient experiences multiple component events only one event counts towards the composite).

Table 5 Primary outcomes at 7 days in PRISM-PLUS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>AGGRASTAT+ Heparin (n=773)</th>
<th>Heparin (n=797)</th>
<th>Risk Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, new MI, and refractory ischemia at 7 days</td>
<td>12.9%</td>
<td>17.9%</td>
<td>32%</td>
<td>0.004</td>
</tr>
<tr>
<td>Death</td>
<td>1.9%</td>
<td>1.9%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>MI</td>
<td>3.9%</td>
<td>7.0%</td>
<td>47%</td>
<td>0.006</td>
</tr>
<tr>
<td>Refractory Ischemia</td>
<td>9.3%</td>
<td>12.7%</td>
<td>30%</td>
<td>0.023</td>
</tr>
</tbody>
</table>

The benefit seen at 7 days was maintained over time. The risk reduction in the composite endpoint at 30 days and 6 months is shown in the Kaplan-Meier curve below.

![Kaplan-Meier curve](image)

Figure 1. Time to first event of death, new MI, or refractory ischemia in PRISM-PLUS

An analysis of the results by sex suggests that women who are medically managed or who undergo subsequent PTCA/atherectomy may receive less benefit from AGGRASTAT (95% confidence limits for relative risk of 0.61-1.74) than do men (0.43-0.89) (p=0.11). This difference may be a true treatment difference, the effect of other differences in these subgroups, or a chance occurrence.

Approximately 90% of patients in the PRISM-PLUS study underwent coronary angiography and 30% underwent angioplasty/atherectomy during the first 30 days of the study. The majority of these patients continued on study drug throughout these procedures. AGGRASTAT was continued for 12-24 hours (average 15 hours) after angioplasty/atherectomy. The effects of AGGRASTAT at Day 30 did not appear to differ among sub-populations that did or did not receive PTCA or CABG, both prior to and after the procedure.

**PRISM (Platelet Receptor Inhibition for Ischemic Syndrome Management)**

In the PRISM study, a randomized, parallel, double-blind study, 3232 patients with NSTE-ACS intended to be managed without coronary intervention were randomized to AGGRASTAT (initial dose of 0.6 mcg/kg/min for 30 minutes followed by 0.15 mcg/kg/min for 47.5 hours) or heparin (5000-unit intravenous bolus followed by an infusion of 1000 U/h for 48 hours). The mean age of the population was 62 years; 32% of the population was female and 25% had non-ST elevation MI on presentation. Thirty percent had no ECG evidence of cardiac ischemia. Exclusion criteria were similar to PRISM-PLUS. The primary endpoint was the composite endpoint of refractory ischemia, MI or death at the end of the 48-hour drug infusion. The results are shown in Table 6.

Table 6 Primary outcomes in PRISM – Cardiac Ischemia Events

<table>
<thead>
<tr>
<th>Composite Endpoint (death, MI, or refractory ischemia) (n=1616)</th>
<th>AGGRASTAT (n=1616)</th>
<th>Heparin (n=1616)</th>
<th>Risk Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Days (end of drug infusion)</td>
<td>3.8%</td>
<td>5.6%</td>
<td>33%</td>
<td>0.015</td>
</tr>
<tr>
<td>7 Days</td>
<td>10.3%</td>
<td>11.3%</td>
<td>10%</td>
<td>0.33</td>
</tr>
</tbody>
</table>

In the PRISM study, no adverse effect of AGGRASTAT on mortality at either 7 or 30 days was detected. This result is different from that in the PRISM-PLUS study, where the arm that included AGGRASTAT without heparin (n=345) was dropped at an interim analysis by the Data Safety Monitoring Committee for increased mortality at 7 days.
16 HOW SUPPLIED/STORAGE AND HANDLING

AGGRASTAT is supplied as a clear, non-preserved, colorless, isosmotic, sterile premixed solution with sodium chloride for tonicity adjustment.

Table 7 AGGRASTAT product details

<table>
<thead>
<tr>
<th>Strength</th>
<th>Total Amount</th>
<th>Packaging</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mcg/mL</td>
<td>5 mg/100 mL</td>
<td>bag</td>
<td>25208-002-01</td>
</tr>
<tr>
<td>50 mcg/mL</td>
<td>12.5 mg/250 mL</td>
<td>bag</td>
<td>25208-002-02</td>
</tr>
<tr>
<td>50 mcg/mL</td>
<td>5 mg/100 mL</td>
<td>vial</td>
<td>25208-002-03</td>
</tr>
<tr>
<td>250 mcg/mL</td>
<td>3.75 mg/15 mL</td>
<td>bolus vial</td>
<td>25208-001-04</td>
</tr>
</tbody>
</table>

FOR INTRAVENOUS USE ONLY

Store AGGRASTAT at controlled room temperature, 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) [see USP]. Do not freeze. Protect from light during storage.

17 PATIENT COUNSELING INFORMATION

Advise patients to watch closely for any signs of bleeding or bruising and to report these to their health care provider when they occur.

Advise patients to discuss with their health care provider their use of any other medications, including over-the-counter or herbal products prior to AGGRASTAT use.

Patent: www.medicure.com/aggrastat/patents

AGGRASTAT is manufactured for:

MEDICURE INTERNATIONAL, INC.

By:

BAXTER HEALTHCARE CORPORATION

Deerfield, Illinois 60015 USA

And

EMERGENT BIOSOLUTIONS

Baltimore, Maryland 21230 USA

Distributed by:

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Printed in USA

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