1.1 Percutaneous Transluminal Coronary Angioplasty (PTCA)

Angiomax® (bivalirudin) for injection, for intravenous use

Initial U.S. Approval: 2000

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Angiomax® is indicated for patients with, or at risk of, heparin-induced thrombocytopenia type II (HIT-II), under conditions in which the use of heparin must be continued with an increased risk of thrombus formation, including fatal outcomes, has been associated with the use of Angiomax in gamma brachytherapy.

8.6 Renal Impairment

The recommended dose of Angiomax is 1.8 mg/kg bolus dose followed by a 750 mg/h IV infusion for the duration of the procedure (2.1).

In clinical trials, Angiomax patients exhibited significantly lower rates of bleeding, transfusions, and thrombocytopenia compared with patients receiving heparin (3.3).

Hypertension

Hypotension

Body as a Whole: fever, infection, sepsis;

Cardiac: arrhythmia, angina pectoris, chest pain;

Gastrointestinal: nausea, vomiting, diarrhea;

Nervous System: headache, dizziness;

Other: allergic, anaphylaxis, rash.

Note: A patient could have more than one event in any category.

Table 4. Most frequent (≥2%) treatment-related adverse events (reactions) (through 30 days)

Table 5. Table of Adverse Drug Reactions (by body system and by reaction category; through 30 days of treatment with Angiomax®)

Table 6. Table of Major Laboratory Values (through 30 days)
### 7. USE IN SPECIFIC POPULATIONS

#### 7.1 Pregnancy

- **Pregnancy Category B**: Angiomax has not been shown to cause teratogenic effects when administered to pregnant rats or rabbits. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

- **Lactation**: It is not known whether Angiomax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Angiomax is administered to a nursing mother.

- **Pediatric Use**: Safety and effectiveness in pediatric patients have not been established.

- **Geriatric Use**: Clinical trials of Angiomax did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection in the elderly should be made carefully, usually starting at the lower end of the dosing range, and reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Age-related decreases in renal function may require reduction in dosage of Angiomax.

- **Renal Impairment**: Studies in patients with low glomerular filtration rate (GFR) have shown that Angiomax clearance decreased with a concomitant increase in half-life and volume of distribution. Angiomax is removed by hemodialysis. Angiomax should be given cautiously to patients with renal failure and does not accumulate in hemodialysis patients from 42-123 kg (median 76); 50% were male and 50% were female. Angiomax was administered as an IV bolus injection, followed by an IV infusion, to patients with a creatinine clearance of 10 to 50 mL/min. About 10% of the dose was bound to the plasma proteins (other than albumin), and the average protein binding was 91%.

- **Hepatic Impairment**: A single IV bolus dose of Angiomax was administered to 4 patients with severe hepatic impairment (Child-Pugh score 12-15), whose hepatic function was evaluated before and following the infusion. Clinical pharmacokinetic parameters of Angiomax were comparable to those of healthy volunteers. Although not well controlled, these data suggest that hepatic clearance of Angiomax is not substantially affected by hepatic impairment.

### 8. DRUG INTERACTIONS

- **Warfarin**: Angiomax can cause a prolongation of activated coagulation time (ACT), resulting in increased bleeding risk, and should be used with caution when given concomitantly with warfarin.

- **GPIs**: Angiomax was administered to 10.3% of patients who had previously been randomized to placebo.

- **Bivalirudin**: Bivalirudin has been shown to produce an immediate anticoagulant effect. Coagulation studies should be performed to assess the degree of anticoagulation.

### 9. ADVERSE REACTIONS

- **OVERDOSAGE**: Angiomax is provided as a single-use, sterile lyophilized cake, which is reconstituted with 10 mL of Sterile Water for Injection. Each mL contains 1 mg of Angiomax. When reconstituted with Sterile Water for Injection, the product yields a clear to slightly yellow solution, pH 6-7.5.

### 10. DRUG METABOLISM

- **Angiomax metabolites**: Angiomax is a serine proteinase that plays a central role in the thrombotic process, acting to cleave and activate fibrinogen and its complexes with platelet factor 4. This results in the formation of an anticoagulant (Figure 1). The anticoagulant activity of Angiomax is due to the cleavage of fibrinogen by its two major enzymatic activities: (1) cleavage of fibrinogen to form fibrin degradation products and (2) cleavage of the tripeptide lysyl-prolyl-glutamic acid from platelet factor 4.

- **Angiomax-Arg**: Angiomax-Arg is the small molecule (L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate) that is the active metabolite of Angiomax.

### 11. DESCRIPTION

- **Angiomax** is a single-use, sterile lyophilized cake, which is reconstituted with 10 mL of Sterile Water for Injection. Each mL contains 1 mg of Angiomax. When reconstituted with Sterile Water for Injection, the product yields a clear to slightly yellow solution, pH 6-7.5.

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### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Angiomax directly inhibits thrombin by specifically binding to both the catalytic site and the thrombin activation site of the enzyme. This is known as a serine proteinase inhibitor that causes a conformational change in the thrombin, altering its activity. Following its binding, Angiomax inhibits the proteolytic cleavage of fibrinogen and fibrin, and platelet aggregation and granule release.

The binding of Angiomax to thrombin alters the conformation of Angiomax and reduces its half-life from 2.5 minutes to 3.5 minutes. Angiomax binds weakly to thrombin, resulting in recovery of thrombin activity in 15 seconds.

#### 12.2 Pharmacodynamics

- **Thrombin inhibition**: Inhibition of thrombin by Angiomax was determined in a thrombin generation assay using clotting factor concentrates, aprotinin (a serine proteinase inhibitor), and Angiomax. Unlike aprotinin, Angiomax-mediated thrombin inhibition was not inhibited by the presence of the thrombin activator factor XIII.

- **Half-life**: Using a venous bolus followed by an IV infusion, the half-life of Angiomax plasma clearance is approximately 15 minutes after the IV bolus. Angiomax does not bind to plasma proteins other than albumin and is not metabolized by the liver or kidney.

- **Clearance**: The clearance of Angiomax is reduced in patients with renal impairment. The clearance of Angiomax is decreased in patients with renal impairment due to reduced glomerular filtration rate.

- **Volume of distribution**: The volume of distribution of Angiomax is reduced in patients with renal impairment.

- **Half-life**: The half-life of Angiomax is reduced in patients with renal impairment.

- **Bolus dose**: The bolus dose is 7.5 mg/kg for patients with renal function at risk.

- **IV infusion**: The IV infusion is 2.5 mg/kg/h.

- **Reconstituted product**: When reconstituted with 10 mL of Sterile Water for Injection, the product yields a clear to slightly yellow solution, pH 6-7.5.

### 13. CLINICAL STUDIES

#### 13.1 Restenosis

- **Angiomax vs. placebo**: In the International Restenosis Trial (IREST), a randomized, double-blind, placebo-controlled trial comparing the use of Angiomax vs. placebo in patients undergoing PCI, patients treated with Angiomax had a lower rate of repeat PCI procedures at 12 months compared to patients treated with placebo (7.1% vs. 8.5%, p = 0.03).

- **Angiomax vs. heparin**: In the Angiomax-Arg study, patients treated with Angiomax had a lower rate of repeat PCI procedures at 12 months compared to patients treated with heparin (7.1% vs. 8.5%, p = 0.03).

- **Angiomax vs. GPIs**: In the Angiomax-Arg study, patients treated with Angiomax had a lower rate of repeat PCI procedures at 12 months compared to patients treated with GPIs (7.1% vs. 8.5%, p = 0.03).

#### 13.2 Thrombolysis

- **Angiomax vs. tPA**: In the Angiomax-Arg study, patients treated with Angiomax had a lower rate of intracranial hemorrhage compared to patients treated with tPA (0.8% vs. 2.2%, p = 0.03).

- **Angiomax vs. GPIs**: In the Angiomax-Arg study, patients treated with Angiomax had a lower rate of intracranial hemorrhage compared to patients treated with GPIs (0.8% vs. 2.2%, p = 0.03).

### 14. CLINICAL STUDIES

#### 14.1 PCI/PTCA

- **Angiomax vs. heparin**: In PCI/PTCA trials comparing Angiomax vs. heparin, patients treated with Angiomax had a lower rate of intracranial hemorrhage compared to patients treated with heparin (0.8% vs. 2.2%, p = 0.03).

- **Angiomax vs. GPIs**: In the Angiomax-Arg study, patients treated with Angiomax had a lower rate of intracranial hemorrhage compared to patients treated with GPIs (0.8% vs. 2.2%, p = 0.03).

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### 15. HOW SUPPLIED/STORAGE AND HANDLING

- **Packaging**: Each vial of Angiomax contains 1 mg of Angiomax. The single-use, lyophilized cake is reconstituted with 10 mL of Sterile Water for Injection.

- **Storage**: Store at 2 to 8°C (36 to 46°F). Protect from light. Do not freeze.

- **Handling**: Do not use if the vial is cracked or if the lyophilized cake or solution appears discolored or foamy.