

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Bivalirudin for Injection safely and effectively. See full prescribing information for Bivalirudin for Injection.

Bivalirudin for Injection, Powder, Lyophilized, for Solution for Intravenous Use

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Bivalirudin is a direct thrombin inhibitor indicated for use as an anticoagulant in patients:

- With unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). (1.1)
- Undergoing percutaneous coronary intervention (PCI) with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as in the REPLACE-2 study. (1.2)
- With, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITS), undergoing PCI. (1.2)

Bivalirudin is intended for use with aspirin. (1.3)

Limitation of use

Safety and effectiveness not established in patients with acute coronary syndromes who are not undergoing PTCA or PCI. (1.4)

DOSAGE AND ADMINISTRATION

For patients who do not have HIT/HITS

- PCI/PTCA: 0.75 mg/kg intravenous (IV) bolus dose followed by a 1.75 mg/kg/h IV infusion for the duration of the procedure. (2.1)
- Perform activated clotting time (ACT) test 5 minutes post-bolus dose. If needed, give an additional bolus of 0.3 mg/kg. (2.1)
- After PCI/PTCA, IV infusion may be continued for up to 4 hours, after which a rate of 0.2 mg/kg/h can be used for up to 20 more hours, if needed. (2.1)
- Consider glycoprotein IIb/IIIa inhibitor (GPI) administration with procedural complications. (2.1, 14.1)

For patients who have HIT/HITS

- The recommended dose of bivalirudin in patients with HIT/HITS undergoing PCI is an IV bolus of 0.75 mg/kg. This should be followed

by an infusion at a rate of 1.75 mg/kg/h for the duration of the procedure. (2.1)

- After PCI/PTCA, IV infusion may be continued for up to 4 hours, after which a rate of 0.2 mg/kg/h can be used for up to 20 more hours, if needed. (2.1)

For patients with renal impairment

- No reduction in bolus dose required. Consider reduction of the rate of infusion to 1 mg/kg/h for CrCL <30 mL/min or 0.25 mg/kg/h if on dialysis. (2.2)

DOSAGE FORMS AND STRENGTHS

Vials containing 250 mg of bivalirudin as a sterile, lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

- Active major bleeding (4)
- Hypersensitivity to bivalirudin or any product components (4)

WARNINGS AND PRECAUTIONS

- Bleeding events: Hemorrhage can occur at any site. Discontinue bivalirudin for an unexplained fall in blood pressure or hematocrit. (5.1)
- Coronary artery brachytherapy: Risk of thrombus formation, including fatal outcomes, in gamma brachytherapy. (5.2)

ADVERSE REACTIONS

Most common adverse reaction was bleeding (28%). Other adverse reactions (incidence >0.5%) were headache, thrombocytopenia and fever. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Heparin, warfarin, thrombolytics, or GPIs: Increased major bleeding risk with concomitant use. (7)

USE IN SPECIFIC POPULATIONS

- Pediatric patients: Safety and efficacy not established. (8.4)
- Geriatric patients: Elderly patients may experience more bleeding than younger patients. (8.5)
- Renal impairment: Reduce infusion dose and monitor ACT. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Percutaneous Transluminal Coronary Angioplasty (PTCA)

Bivalirudin is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

1.2 Percutaneous Coronary Intervention (PCI)

Bivalirudin with provisional use of glycoprotein IIb/IIIa inhibitor (GPI) as listed in the REPLACE-2 trial [see *Clinical Studies (14.1)*] is indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI).

Bivalirudin is indicated for patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI.

1.3 Use with Aspirin

Bivalirudin in these indications is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin [see *Dosage and Administration (2.1)* and *Clinical Studies (14.1)*].

1.4 Limitation of Use

The safety and effectiveness of bivalirudin have not been established in patients with acute coronary syndromes who are not undergoing PTCA or PCI.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Bivalirudin is for intravenous administration only.

Bivalirudin is intended for use with aspirin (300-325 mg daily) and has been studied only in patients receiving concomitant aspirin.

For patients who do not have HIT/HITTS

The recommended dose of bivalirudin is an intravenous (IV) bolus dose of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h for the duration of the PCI/PTCA procedure. Five min after the bolus dose has been administered, an activated clotting time (ACT) should be performed and an additional bolus of 0.3 mg/kg should be given if needed.

GPI administration should be considered in the event that any of the conditions listed in the REPLACE-2 clinical trial description [see *Clinical Studies (14.1)*] is present.

For patients who have HIT/HITTS

The recommended dose of bivalirudin in patients with HIT/HITTS undergoing PCI is an IV bolus of 0.75 mg/kg. This should be followed by a continuous infusion at a rate of 1.75 mg/kg/h for the duration of the procedure.

For ongoing treatment post procedure

Continuation of the bivalirudin infusion following PCI/PTCA for up to 4 hours post-procedure is optional, at the discretion of the treating physician. After four hours, an additional IV infusion of bivalirudin may be initiated at a rate of 0.2 mg/kg/h (low-rate infusion), for up to 20 hours, if needed.

2.2 Dosing in Renal Impairment

No reduction in the bolus dose is needed for any degree of renal impairment. The infusion dose of bivalirudin may need to be reduced, and anticoagulant status monitored in patients with renal impairment. Patients with moderate renal impairment (30-59 mL/min) should receive an infusion of 1.75 mg/kg/h. If the creatinine clearance is less than 30 mL/min, reduction of the infusion rate to 1 mg/kg/h should be considered. If a patient is on hemodialysis, the infusion rate should be reduced to 0.25 mg/kg/h [*see Use In Specific Population (8.6)*].

2.3 Instructions for Administration

Bivalirudin is intended for intravenous bolus injection and continuous infusion after reconstitution and dilution. To each 250 mg vial, add 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 50 mL of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 5 mg/mL (e.g., 1 vial in 50 mL; 2 vials in 100 mL; 5 vials in 250 mL). The dose to be administered is adjusted according to the patient's weight (see Table 1).

If the low-rate infusion is used after the initial infusion, a lower concentration bag should be prepared. In order to prepare this bag, reconstitute the 250 mg vial with 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 500 mL of 5% Dextrose in Water or 0.9% Sodium Chloride for Injection to yield a final concentration of 0.5 mg/mL. The infusion rate to be administered should be selected from the right-hand column in Table 1.

Table 1. Dosing Table

Weight (kg)	Using 5 mg/mL Concentration		Using 0.5 mg/mL Concentration
	Bolus 0.75 mg/kg (mL)	Infusion 1.75 mg/kg/h (mL/h)	Subsequent Low-rate Infusion 0.2 mg/kg/h (mL/h)
43-47	7	16	18
48-52	7.5	17.5	20
53-57	8	19	22
58-62	9	21	24
63-67	10	23	26
68-72	10.5	24.5	28
73-77	11	26	30
78-82	12	28	32
83-87	13	30	34
88-92	13.5	31.5	36
93-97	14	33	38
98-102	15	35	40
103-107	16	37	42
108-112	16.5	38.5	44
113-117	17	40	46
118-122	18	42	48
123-127	19	44	50
128-132	19.5	45.5	52
133-137	20	47	54
138-142	21	49	56
143-147	22	51	58
148-152	22.5	52.5	60

Bivalirudin should be administered via an intravenous line. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets. The following drugs should **not** be administered in the same intravenous line with bivalirudin, since they resulted in haze formation, microparticulate formation, or gross precipitation when mixed with bivalirudin: alteplase, amiodarone HCl, amphotericin B, chlorpromazine HCl, diazepam, prochlorperazine edisylate, reteplase, streptokinase, and vancomycin HCl. Dobutamine was compatible at concentrations up to 4 mg/mL but incompatible at a concentration of 12.5 mg/mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Preparations of bivalirudin containing particulate matter should not be used. Reconstituted material will be a clear to slightly opalescent, colorless to slightly yellow solution.

2.4 Storage after Reconstitution

Do not freeze reconstituted or diluted bivalirudin. Reconstituted material may be stored at 2-8°C for up to 24 hours. Diluted bivalirudin with a concentration of between 0.5 mg/mL and 5 mg/mL is stable at room temperature for up to 24 hours. Discard any unused portion of reconstituted solution remaining in the vial.

3 DOSAGE FORMS AND STRENGTHS

Bivalirudin is supplied as a sterile, lyophilized powder in single-use, glass vials. After reconstitution, each vial delivers 250 mg of Bivalirudin.

4 CONTRAINDICATIONS

Bivalirudin is contraindicated in patients with:

- Active major bleeding;
- Hypersensitivity (e.g., anaphylaxis) to bivalirudin or its components [*see Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding Events

Although most bleeding associated with the use of bivalirudin in PCI/PTCA occurs at the site of arterial puncture, hemorrhage can occur at any site. An unexplained fall in blood pressure or hematocrit should lead to serious consideration of a hemorrhagic event and cessation of bivalirudin administration [*see Adverse Reactions (6.1)*]. Bivalirudin should be used with caution in patients with disease states associated with an increased risk of bleeding.

5.2 Coronary Artery Brachytherapy

An increased risk of thrombus formation, including fatal outcomes, has been associated with the use of bivalirudin in gamma brachytherapy.

If a decision is made to use bivalirudin during brachytherapy procedures, maintain meticulous catheter technique, with frequent aspiration and flushing, paying special attention to minimizing conditions of stasis within the catheter or vessels [*see Adverse Reactions (6.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials 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 practice.

Bleeding

In 6010 patients undergoing PCI treated in the REPLACE-2 trial, bivalirudin patients exhibited statistically significantly lower rates of bleeding, transfusions, and thrombocytopenia as noted in Table 2.

Table 2. Major Hematologic Outcomes REPLACE-2 Study (Safety Population)

	BIVALIRUDIN with “Provisional” GPI¹ (N = 2914)	HEPARIN+GPI (N = 2987)	p-value
Protocol defined major hemorrhage² (%)	2.3%	4.0%	<0.001
Protocol defined minor hemorrhage³ (%)	13.6%	25.8%	<0.001
TIMI defined bleeding⁴			
-Major	0.6%	0.9%	0.259
-Minor	1.3%	2.9%	<0.001
Non-access site bleeding:			
-Retroperitoneal bleeding	0.2%	0.5%	0.069
-Intracranial bleeding	<0.1%	0.1%	1.0
Access site bleeding			
-Sheath site bleeding	0.9%	2.4%	<0.001
Thrombocytopenia⁵			
<100,000	0.7%	1.7%	<0.001
<50,000	0.3%	0.6%	0.039
Transfusions			
-RBC	1.3%	1.9%	0.08
-Platelets	0.3%	0.6%	0.095

¹ GPIs were administered to 7.2% of patients in the bivalirudin with provisional GPI group.

² Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, a transfusion of ≥ 2 units of blood/blood products, a fall in hemoglobin >4 g/dL, whether or not bleeding site is identified, spontaneous or non-spontaneous blood loss with a decrease in hemoglobin >3 g/dL.

³ Defined as observed bleeding that does not meet the criteria for major hemorrhage.

⁴ TIMI major bleeding is defined as: intracranial, or a fall in adjusted Hgb >5 g/dL or Hct of $>15\%$; TIMI minor bleeding is defined as a fall in adjusted Hgb of 3 to <5 g/dL or a fall in adjusted Hct of 9 to $<15\%$, with a bleeding site such as hematuria, hematemesis, hematomas, retroperitoneal bleeding or a decrease in Hgb of >4 g/dL with no bleeding site.

⁵ If $<100,000$ and $>25\%$ reduction from baseline, or $<50,000$.

In 4312 patients undergoing PTCA for treatment of unstable angina in 2 randomized, double-blind studies comparing bivalirudin to heparin, bivalirudin patients exhibited lower rates of major bleeding and lower requirements for blood transfusions. The incidence of major bleeding is presented in Table 3. The incidence of major bleeding was lower in the bivalirudin group than in the heparin group.

Table 3. Major Bleeding and Transfusions in BAT Trial (All Patients)¹

	BIVALIRUDIN N = 2161	HEPARIN N = 2151
No. (%) Patients with Major Hemorrhage ²	79 (3.7)	199 (9.3)
- with ≥ 3 g/dL fall in Hgb	41 (1.9)	124 (5.8)
- with ≥ 5 g/dL fall in Hgb	14 (0.6)	47 (2.2)
- Retroperitoneal bleeding	5 (0.2)	15 (0.7)
- Intracranial bleeding	1 (<0.1)	2 (<0.1)
- Required transfusion	43 (2.0)	123 (5.7)

¹ No monitoring of ACT (or PTT) was done after a target ACT was achieved.

² Major hemorrhage was defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥ 3 g/dL or leading to a transfusion of ≥ 2 units of blood. This table includes data from the entire hospitalization period.

In the AT-BAT study, of the 51 patients with HIT/HITTS, 1 patient who did not undergo PCI had major bleeding during CABG on the day following angiography. Nine patients had minor bleeding (mostly due to access site bleeding), and 2 patients developed thrombocytopenia.

Other Adverse Reactions

Adverse reactions, other than bleeding, observed in clinical trials were similar between the bivalirudin treated patients and the control groups.

Adverse reactions (related adverse events) seen in clinical studies in patients undergoing PCI and PTCA are shown in Tables 4 and 5.

Table 4. Most Frequent ($\geq 0.2\%$) Treatment-Related Adverse Events (Reactions) (Through 30 Days) in the REPLACE-2 Safety Population

	BIVALIRUDIN with “Provisional” GPI¹	HEPARIN+GPI
	(N = 2914)	(N = 2987)
	n (%)	n (%)
Patients with at least one treatment-related AE	78 (2.7)	115 (3.9)
Thrombocytopenia	9 (0.3)	30 (1.0)
Nausea	15 (0.5)	7 (0.2)
Hypotension	7 (0.2)	11 (0.4)
Angina pectoris	5 (0.2)	12 (0.4)
Headache	6 (0.2)	5 (0.2)
Injection site pain	3 (0.1)	8 (0.3)
Nausea and vomiting	2 (0.1)	6 (0.2)
Vomiting	3 (0.1)	5 (0.2)

NOTE: A patient could have more than one event in any category.
Abbreviation: AE = adverse event.

Table 5. Adverse Events Other Than Bleeding Occurring In \geq 5% Of Patients In Either Treatment Group In BAT Trial

EVENT	Treatment Group	
	BIVALIRUDIN N = 2161	HEPARIN N = 2151
	Number of Patients (%)	
CARDIOVASCULAR		
Hypotension	262 (12)	371 (17)
Hypertension	135 (6)	115 (5)
Bradycardia	118 (5)	164 (8)
GASTROINTESTINAL		
Nausea	318 (15)	347 (16)
Vomiting	138 (6)	169 (8)
Dyspepsia	100 (5)	111 (5)
GENITOURINARY		
Urinary retention	89 (4)	98 (5)
MISCELLANEOUS		
Back pain	916 (42)	944 (44)
Pain	330 (15)	358 (17)
Headache	264 (12)	225 (10)
Injection site pain	174 (8)	274 (13)
Insomnia	142 (7)	139 (6)
Pelvic pain	130 (6)	169 (8)
Anxiety	127 (6)	140 (7)
Abdominal pain	103 (5)	104 (5)
Fever	103 (5)	108 (5)
Nervousness	102 (5)	87 (4)

Serious, non-bleeding adverse events were experienced in 2% of 2161 bivalirudin-treated patients and 2% of 2151 heparin-treated patients. The following individual serious non-bleeding adverse events were rare ($>0.1\%$ to $<1\%$) and similar in incidence between bivalirudin- and heparin-treated patients. These events are listed by body system: *Body as a Whole*: fever, infection, sepsis; *Cardiovascular*: hypotension, syncope, vascular anomaly, ventricular fibrillation; *Nervous*: cerebral ischemia, confusion, facial paralysis; *Respiratory*: lung edema; *Urogenital*: kidney failure, oliguria. In the BAT trial, there was no causality assessment for adverse events.

6.2 Immunogenicity/Re-Exposure

In *in vitro* studies, bivalirudin exhibited no platelet aggregation response against sera from patients with a history of HIT/HITTS.

Among 494 subjects who received bivalirudin in clinical trials and were tested for antibodies, 2 subjects had treatment-emergent positive bivalirudin antibody tests. Neither subject demonstrated clinical evidence of allergic or anaphylactic reactions and repeat testing was not performed. Nine additional patients who had initial positive tests were negative on repeat testing.

6.3 Postmarketing Experience

Because postmarketing adverse 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 drug exposure.

The following adverse reactions have been identified during postapproval use of bivalirudin: fatal bleeding; hypersensitivity and allergic reactions including reports of anaphylaxis; lack of anticoagulant effect; thrombus formation during PCI with and without intracoronary brachytherapy, including reports of fatal outcomes.

7 DRUG INTERACTIONS

In clinical trials in patients undergoing PCI/PTCA, co-administration of bivalirudin with heparin, warfarin, thrombolytics, or GPIs was associated with increased risks of major bleeding events compared to patients not receiving these concomitant medications.

There is no experience with co-administration of bivalirudin and plasma expanders such as dextran.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats at subcutaneous doses up to 150 mg/kg/day, (1.6 times the maximum recommended human dose based on body surface area) and rabbits at subcutaneous doses up to 150 mg/kg/day (3.2 times the maximum recommended human dose based on body surface area). These studies revealed no evidence of impaired fertility or harm to the fetus attributable to bivalirudin. There are, however, 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.

Bivalirudin is intended for use with aspirin [*see Indications and Usage (1.3)*]. Because of possible adverse effects on the neonate and the potential for increased maternal bleeding, particularly during the third trimester, bivalirudin and aspirin should be used together during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether bivalirudin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when bivalirudin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of bivalirudin in pediatric patients have not been established.

8.5 Geriatric Use

In studies of patients undergoing PCI, 44% were ≥ 65 years of age and 12% of patients were ≥ 75 years old. Elderly patients experienced more bleeding events than younger patients. Patients treated with bivalirudin experienced fewer bleeding events in each age stratum, compared to heparin.

8.6 Renal Impairment

The disposition of bivalirudin was studied in PTCA patients with mild, moderate and severe renal impairment. The clearance of bivalirudin was reduced approximately 20% in patients with moderate and severe renal impairment and was reduced approximately 80% in dialysis-dependent patients. [*see Clinical Pharmacology (12.3)*].

The infusion dose of bivalirudin may need to be reduced, and anticoagulant status monitored in patients with renal impairment [*see Dosage and Administration (2.2)*].

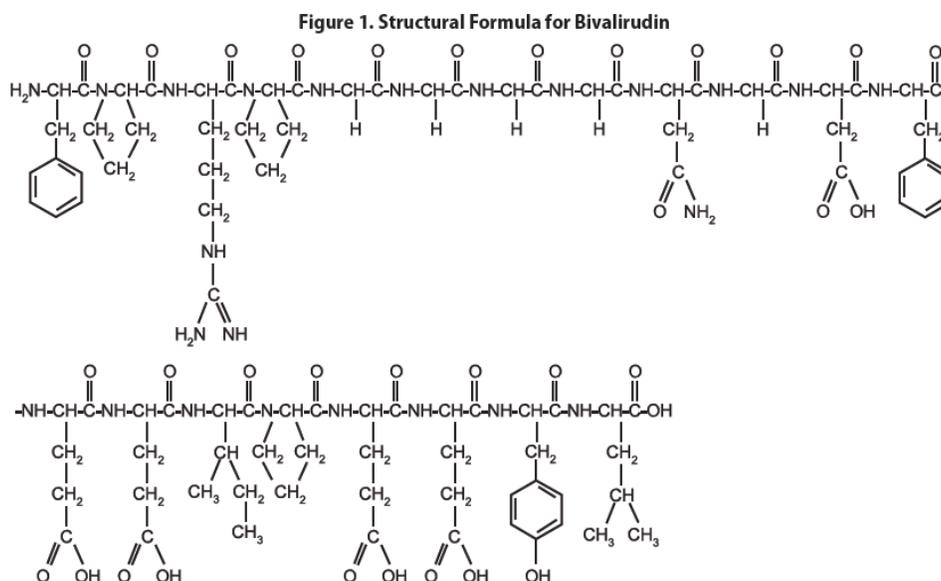
10 OVERDOSAGE

Cases of overdose of up to 10 times the recommended bolus or continuous infusion dose of bivalirudin have been reported in clinical trials and in postmarketing reports. A number of the reported overdoses were due to failure to adjust the infusion dose of bivalirudin in person with renal dysfunction including persons on hemodialysis [see *Dosage and Administration (2.2)*]. Bleeding, as well as deaths due to hemorrhage, have been observed in some reports of overdose. In cases of suspected overdose, discontinue bivalirudin immediately and monitor the patient closely for signs of bleeding. There is no known antidote to bivalirudin. Bivalirudin is hemodialyzable [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Bivalirudin is a specific and reversible direct thrombin inhibitor. The active substance is a synthetic, 20 amino acid peptide. The chemical name is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate (Figure 1). The molecular weight of bivalirudin is 2180 daltons (anhydrous free base peptide).

Bivalirudin is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5-6 (equivalent of approximately 12.5 mg sodium). When reconstituted with Sterile Water for Injection, the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central role in the thrombotic process, acting to cleave fibrinogen into fibrin monomers and to activate Factor XIII to Factor XIIIa, allowing fibrin to develop a covalently cross-linked framework which stabilizes the thrombus; thrombin also activates Factors V and VIII, promoting further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin-Arg₃-Pro₄ bond, resulting in recovery of thrombin active site functions.

In *in vitro* studies, bivalirudin inhibited both soluble (free) and clot-bound thrombin, was not neutralized by products of the platelet release reaction, and prolonged the activated partial thromboplastin time (aPTT), thrombin time (TT), and prothrombin time (PT) of normal human plasma in a concentration-dependent manner. The clinical relevance of these findings is unknown.

12.2 Pharmacodynamics

In healthy volunteers and patients (with $\geq 70\%$ vessel occlusion undergoing routine PTCA), bivalirudin exhibited dose- and concentration-dependent anticoagulant activity as evidenced by prolongation of the ACT, aPTT, PT, and TT. Intravenous administration of bivalirudin produces an immediate anticoagulant effect. Coagulation times return to baseline approximately 1 hour following cessation of bivalirudin administration.

In 291 patients with $\geq 70\%$ vessel occlusion undergoing routine PTCA, a positive correlation was observed between the dose of bivalirudin and the proportion of patients achieving ACT values of 300 sec or 350 sec. At a bivalirudin dose of 1 mg/kg IV bolus plus 2.5 mg/kg/h IV infusion for 4 hours, followed by 0.2 mg/kg/h, all patients reached maximal ACT values >300 sec.

12.3 Pharmacokinetics

Bivalirudin exhibits linear pharmacokinetics following IV administration to patients undergoing PTCA. In these patients, a mean steady state bivalirudin concentration of 12.3 ± 1.7 mcg/mL is achieved following an IV bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h IV infusion. Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells. Bivalirudin is cleared from plasma by a combination of renal mechanisms and proteolytic cleavage, with a half-life in patients with normal renal function of 25 min.

The disposition of bivalirudin was studied in PTCA patients with mild, moderate, and severe renal impairment. Drug elimination was related to glomerular filtration rate (GFR). Total body clearance was similar for patients with normal renal function and with mild renal impairment (60-89 mL/min). Clearance was reduced in patients with moderate and severe renal impairment and in dialysis-dependent patients (See Table 6 for pharmacokinetic parameters).

Bivalirudin is hemodialyzable, with approximately 25% cleared by hemodialysis.

Table 6. PK Parameters in Patients with Renal Impairment*

Renal Function (GFR, mL/min)	Clearance (mL/min/kg)	Half-life (min)
Normal renal function (≥ 90 mL/min)	3.4	25
Mild renal impairment (60-89 mL/min)	3.4	22
Moderate renal impairment (30-59 mL/min)	2.7	34
Severe renal impairment (10-29 mL/min)	2.8	57
Dialysis-dependent patients (off dialysis)	1.0	3.5 hours

* The ACT should be monitored in renally-impaired patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of bivalirudin. Bivalirudin displayed no genotoxic potential in the *in vitro* bacterial cell reverse mutation assay (Ames test), the *in vitro* Chinese hamster ovary cell forward gene mutation test (CHO/HGPRT), the *in vitro* human lymphocyte chromosomal aberration assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, and the *in vivo* rat micronucleus assay. Fertility and general reproductive performance in rats were unaffected by subcutaneous doses of bivalirudin up to 150 mg/kg/day, about 1.6 times the dose on a body surface area basis (mg/m²) of a 50 kg person given the maximum recommended dose of 15 mg/kg/day.

14 CLINICAL STUDIES

14.1 PCI/PTCA

Bivalirudin has been evaluated in five randomized, controlled interventional cardiology trials reporting 11,422 patients. Stents were deployed in 6062 of the patients in these trials – mainly in trials performed since 1995. Percutaneous transluminal coronary angioplasty, atherectomy or other procedures were performed in the remaining patients.

REPLACE-2 Trial

This was a randomized, double-blind, multicenter study reporting 6002 (intent-to-treat) patients undergoing PCI. Patients were randomized to treatment with bivalirudin with the “provisional” use of platelet glycoprotein IIb/IIIa inhibitor (GPI) or heparin plus planned use of GPI. GPIs were added on a “provisional” basis to patients who were randomized to bivalirudin in the following circumstances:

- decreased TIMI flow (0 to 2) or slow reflow;
- dissection with decreased flow;
- new or suspected thrombus;
- persistent residual stenosis;
- distal embolization;
- unplanned stent;
- suboptimal stenting;
- side branch closure;
- abrupt closure; clinical instability; and
- prolonged ischemia.

During the study, one or more of these circumstances occurred in 12.7% of patients in the bivalirudin with provisional GPI arm. GPIs were administered to 7.2% of patients in the bivalirudin with provisional GPI arm (62.2% of eligible patients).

Patients ranged in age from 25-95 years (median, 63); weight ranged from 35-199 kg (median 85.5); 74.4% were male and 25.6% were female. Indications for PCI included unstable angina (35% of patients), myocardial infarction within 7 days prior to intervention (8% of patients), stable angina (25%) and positive ischemic stress test (24%). Stents were deployed in 85% of patients. Ninety-nine percent of patients received aspirin and 86% received thienopyridines prior to study treatment.

Bivalirudin was administered as a 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion for the duration of the procedure. The activated clotting time (ACT – measured by a Hemochron[®] device) was measured 5 min after the first bolus of study medication. If the ACT was <225 seconds, an additional bolus of 0.3 mg/kg was given. At investigator discretion, the infusion could be continued following the procedure

for up to 4 hours. The median infusion duration was 44 min. Heparin was administered as a 65 U/kg bolus. The activated clotting time (ACT – measured by a Hemochron® device) was measured 5 min after the first bolus of study medication. If the ACT was <225 seconds, an additional bolus of 20 units/kg was given. GPIs (either abciximab or eptifibatide) were given according to manufacturers’ instructions. Both randomized groups could be given “provisional” treatments during the PCI at investigator discretion, but under double-blind conditions. “Provisional” treatment with GPI was requested in 5.2% of patients randomized to heparin plus GPI (they were given placebo) and 7.2% patients randomized to bivalirudin with provisional GPI (they were given abciximab or eptifibatide according to pre-randomization investigator choice and patient stratification).

The percent of patients reaching protocol-specified levels of anticoagulation was greater in the bivalirudin with provisional GPI group than in the heparin plus GPI group. For patients randomized to bivalirudin with provisional GPI, the median 5 min ACT was 358 sec (interquartile range 320-400 sec) and the ACT was <225 sec in 3%. For patients randomized to heparin plus GPI, the median 5 min ACT was 317 sec (interquartile range 263-373 sec) and the ACT was <225 sec in 12%. At the end of the procedure, median ACT values were 334 sec (bivalirudin group) and 276 sec (heparin plus GPI group).

For the composite endpoint of death, MI, or urgent revascularization adjudicated under double-blind conditions, the frequency was higher (7.6%)(95% confidence interval 6.7%-8.6%) in the bivalirudin with “provisional” GPI arm when compared to the heparin plus GPI arm (7.1%) (95% confidence interval 6.1%-8.0%). However, major hemorrhage was reported significantly less frequently in the bivalirudin with provisional GPI arm (2.4%) compared to the heparin plus GPI arm (4.1%). Study outcomes are shown in Table 7.

Table 7. Incidences of Clinical Endpoints at 30 Days for REPLACE-2, a Randomized Double-blind Clinical Trial

Intent-to-treat Population	BIVALIRUDIN with “Provisional” GPI n = 2994	HEPARIN + GPI n = 3008
Efficacy Endpoints		
Death, MI, or urgent revascularization	7.6%	7.1%
Death	0.2%	0.4%
MI	7.0%	6.2%
Urgent revascularization	1.2%	1.4%
Safety Endpoint		
Major hemorrhage ^{*,†}	2.4%	4.1%

* Defined as intracranial bleeding, retroperitoneal bleeding, a transfusion of >2 units of blood/blood products, a fall in Hgb >4 g/dL, whether or not bleeding site is identified, spontaneous or non-spontaneous blood loss with a decrease in Hgb >3 g/dL.

† p-value <0.001 between groups.

At 12 months’ follow-up, mortality was 1.9% among patients randomized to bivalirudin with “provisional” GPIs and 2.5% among patients randomized to heparin plus GPI.

Bivalirudin Angioplasty Trial (BAT)

Bivalirudin was evaluated in patients with unstable angina undergoing PTCA in two randomized, double-blind, multicenter studies with identical protocols. Patients must have had unstable angina defined as: (1) a new onset of severe or accelerated angina or rest pain within the month prior to study entry or (2) angina or ischemic rest pain which developed between four hours and two weeks after an acute myocardial infarction (MI). Overall, 4312 patients with unstable angina, including 741 (17%) patients with post-MI angina, were treated in a 1:1 randomized fashion with bivalirudin or heparin. Patients ranged in age from

29-90 (median 63) years, their weight was a median of 80 kg (39-120 kg), 68% were male, and 91% were Caucasian. Twenty-three percent of patients were treated with heparin within one hour prior to randomization. All patients were administered aspirin 300-325 mg prior to PTCA and daily thereafter. Patients randomized to bivalirudin were started on an intravenous infusion of Angiomax (2.5 mg/kg/h). Within 5 min after starting the infusion, and prior to PTCA, a 1 mg/kg loading dose was administered as an intravenous bolus. The infusion was continued for 4 hours, then the infusion was changed under double-blinded conditions to bivalirudin (0.2 mg/kg/h) for up to an additional 20 hours (patients received this infusion for an average of 14 hours). The ACT was checked at 5 min and at 45 min following commencement. If on either occasion the ACT was <350 sec, an additional double-blinded bolus of placebo was administered. The bivalirudin dose was not titrated to ACT. Median ACT values were: ACT in sec (5th percentile-95th percentile): 345 sec (240-595 sec) at 5 min and 346 sec (range 269-583 sec) at 45 min after initiation of dosing. Patients randomized to heparin were given a loading dose (175 IU/kg) as an intravenous bolus 5 min before the planned procedure, with immediate commencement of an infusion of heparin (15 IU/kg/h). The infusion was continued for 4 hours. After 4 hours of infusion, the heparin infusion was changed under double-blinded conditions to heparin (15 IU/kg/h) for up to 20 additional hours. The ACT was checked at 5 min and at 45 min following commencement. If on either occasion the ACT was <350 sec, an additional double-blind bolus of heparin (60 IU/kg) was administered. Once the target ACT was achieved for heparin patients, no further ACT measurements were performed. All ACTs were determined with the Hemochron[®] device. The protocol allowed use of open-label heparin at the discretion of the investigator after discontinuation of blinded study medication, whether or not an endpoint event (procedural failure) had occurred. The use of open-label heparin was similar between bivalirudin and heparin treatment groups (about 20% in both groups).

The studies were designed to demonstrate the safety and efficacy of bivalirudin in patients undergoing PTCA as a treatment for unstable angina as compared with a control group of similar patients receiving heparin during and up to 24 hours after initiation of PTCA. The primary protocol endpoint was a composite endpoint called procedural failure, which included both clinical and angiographic elements measured during hospitalization. The clinical elements were: the occurrence of death, MI, or urgent revascularization, adjudicated under double-blind conditions. The angiographic elements were: impending or abrupt vessel closure. The protocol-specified safety endpoint was major hemorrhage.

The median duration of hospitalization was 4 days for both the bivalirudin and the heparin treatment groups. The rates of procedural failure were similar in the bivalirudin and heparin treatment groups. Study outcomes are shown in Table 8.

Table 8. Incidences of In-hospital Clinical Endpoints in BAT Trial Occurring within 7 Days

All Patients	BIVALIRUDIN n = 2161	HEPARIN n = 2151
Efficacy Endpoints		
Procedural failure*	7.9%	9.3%
Death, MI, revascularization	6.2%	7.9%
Death	0.2%	0.2%
MI [†]	3.3%	4.2%
Revascularization [‡]	4.2%	5.6%
Safety Endpoint		
Major hemorrhage [§]	3.5%	9.3%

* The protocol-specified primary endpoint (a composite of death or MI or clinical deterioration of cardiac origin requiring revascularization or placement of an aortic balloon pump or angiographic evidence of abrupt vessel closure).

[†] Defined as: Q-wave MI; CK-MB elevation $\geq 2 \times$ ULN, new ST- or T-wave abnormality, and chest pain ≥ 30 min; OR new LBBB with chest pain ≥ 30 min and/or elevated CK-MB enzymes; OR elevated CK-MB and new ST- or T-wave abnormality without chest pain; OR elevated CK-MB.

[‡] Defined as: any revascularization procedure, including angioplasty, CABG, stenting, or placement of an intra-aortic balloon pump.

[§] Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in hemoglobin ≥ 3 g/dL or leading to a transfusion of ≥ 2 units of blood.

AT-BAT Trial

This was a single-group open-label study which enrolled 51 patients with heparin-induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Evidence for the diagnosis of HIT/HITTS was based on a clinical history of a decrease of platelets in patients after heparin administration [new diagnosis or history of clinically suspected or objectively documented HIT/HITTS defined as either: 1) HIT: positive heparin-induced platelet aggregation (HIPA) or other functional assay where the platelet count has decreased to $< 100,000/\text{mL}$ (minimum 30% from prior to heparin), or has decreased to $< 150,000/\text{mL}$ (minimum 40% from prior to heparin), or has decreased as above within hours of receiving heparin in a patient with a recent, previous exposure to heparin; 2) HITTS: thrombocytopenia as above plus arterial or venous thrombosis diagnosed by physician examination/laboratory and/or appropriate imaging studies]. Patients ranged in age from 48-89 years (median 70); weight ranged from 42-123 kg (median 76); 50% were male and 50% were female. Bivalirudin was administered as either 1 mg/kg bolus followed by 2.5 mg/kg/h (high dose in 28 patients) or 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion (lower dose in 25 patients) for up to 4 hours. Ninety-eight percent of patients received aspirin, 86% received clopidogrel and 19% received GPIs.

The median ACT values at the time of device activation were 379 sec (high dose) and 317 sec (lower dose). Following the procedure, 48 of the 51 patients (94%) had TIMI grade 3 flow and stenosis $< 50\%$. One patient died during a bradycardic episode 46 hours after successful PCI, another patient required surgical revascularization, and one patient experienced no flow requiring a temporary intra-aortic balloon.

Two of the fifty-one patients with the diagnosis of HIT/HITTS developed thrombocytopenia after receiving bivalirudin and GPIs.

16 HOW SUPPLIED/STORAGE AND HANDLING

Bivalirudin for Injection is supplied as a sterile, lyophilized powder in single-use, glass vials. After reconstitution, each vial delivers 250 mg of bivalirudin.

Unit of Sale	Concentration	Each
NDC 0409-8300-10 Box containing 10	250 mg/vial	NDC 0409-8300-20 10 mL Single Use Vial

Store Bivalirudin for Injection dosage units at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Advise patients to watch carefully 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 medications or herbal products, prior to bivalirudin use. Examples of other medications that should not be taken with bivalirudin are warfarin and heparin.

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Hospira, Inc., Lake Forest, IL 60045 USA

