BIVALIRUDIN - bivalirudin injection, powder, lyophilized, for solution
Fresenius Kabi USA, LLC

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, for intravenous use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	03/2016
Warnings and Precautions (5.2, 5.4)	03/2016

INDICATIONS AND USAGE

Bivalirudin for Injection 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 (HITTS), undergoing PCI. (1.2)
- Bivalirudin for Injection 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/HITTS
• PCI/PTCA: 0.75 mg/kg intravenous (IV) bolus dose followed immediately by a 1.75 mg/kg/h IV infusion for the duration of the procedure. See FPI for remainder of monitoring and dosing information. (2.1)

For patients who have HIT/HITTS
• PCI: 0.75 mg/kg IV bolus dose followed immediately by a 1.75 mg/kg/h IV infusion for the duration of the procedure. See FPI for remainder of monitoring and dosing information. (2.1)

For patients with STEMI
• Consider extending duration of infusion post-procedure up to 4 hours.

DOSAGE FORMS AND STRENGTHS

For injection: 250 mg of bivalirudin in a single-dose vial 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 Injection for an unexplained fall in blood pressure or hematocrit. (5.1)
• Acute Stent Thrombosis: Increased incidence of acute stent thrombosis in STEMI patients undergoing primary PCI. (2.1, 5.2)
• Coronary artery brachytherapy: Risk of thrombus formation, including fatal outcomes, in gamma brachytherapy. (5.3)
• Laboratory Test Interference: Bivalirudin interferes with INR measurements. (5.4)

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 Fresenius Kabi USA, LLC at 1-800-551-7176 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

• *Geriatric patients:* Increased bleeding risk possible. (8.5)
• *Renal impairment:* Reduce infusion dose and monitor ACT. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Percutaneous Transluminal Coronary Angioplasty (PTCA)

Bivalirudin for Injection 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 for Injection 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 for Injection 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 for Injection 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 for Injection 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 for Injection is for intravenous administration only.

Bivalirudin for Injection is intended for use with aspirin (300 to 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 for Injection is an intravenous (IV) bolus dose of 0.75 mg/kg, followed immediately 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 for Injection 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

Bivalirudin for Injection infusion may be continued following PCI/PTCA for up to 4 hours post-procedure at the discretion of the treating physician.

In patients with ST segment elevation myocardial infarction (STEMI) continuation of the Bivalirudin for Injection infusion at a rate of 1.75 mg/kg/h following PCI/PTCA for up to 4 hours post-procedure should be considered to mitigate risk of stent thrombosis. *[see Warnings and Precautions (5.2)]*.

After four hours, an additional IV infusion of Bivalirudin for Injection 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 for Injection may need to be reduced, and anticoagulant status monitored in patients with renal impairment. Patients with moderate renal impairment (30 to 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 Populations (8.6)]*.

2.3 Instructions for Administration

Bivalirudin for Injection 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. Next, withdraw and discard 5 mL from a 50 mL infusion bag containing 5% Dextrose in Water or 0.9% Sodium Chloride for Injection. Then add the contents of the reconstituted vial to the infusion bag containing 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 lower concentration, reconstitute the 250 mg vial with 5 mL of Sterile Water for Injection, USP. Gently swirl until all material is dissolved. Next, withdraw and discard 5 mL from a 500 mL infusion bag containing 5% Dextrose in Water or 0.9% Sodium Chloride for Injection. Then add the contents of the reconstituted vial to the infusion bag containing 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

	Using 5 mg/mL Concentration		**Using 0.5 mg/mL Concentration**
Weight (kg)	**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 to 47	7	16	18
48 to 52	7.5	17.5	20
53 to 57	8	19	22
58 to 62	9	21	24
63 to 67	10	23	26
68 to 72	10.5	24.5	28
73 to 77	11	26	30
78 to 82	12	28	32
83 to 87	13	30	34

88 to 92	13.5	31.5	36
93 to 97	14	33	38
98 to 102	15	35	40
103 to 107	16	37	42
108 to 112	16.5	38.5	44
113 to 117	17	40	46
118 to 122	18	42	48
123 to 127	19	44	50
128 to 132	19.5	45.5	52
133 to 137	20	47	54
138 to 142	21	49	56
143 to 147	22	51	58
148 to 152	22.5	52.5	60

Bivalirudin for Injection 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 for Injection, since they resulted in haze formation, microparticulate formation, or gross precipitation when mixed with Bivalirudin for Injection: 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 for Injection 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 for Injection. Reconstituted material may be stored at 2 to 8°C for up to 24 hours. Diluted Bivalirudin for Injection 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

For injection: 250 mg of bivalirudin in a single-dose vial for reconstitution. Each vial contains 250 mg of bivalirudin equivalent to an average of 270 mg bivalirudin trifluoroacetate*. Following reconstitution with Sterile Water for Injection, the product is a clear to opalescent, colorless to slightly yellow solution, pH 5 to 6.

**The range of bivalirudin trifluoroacetate is 260 to 280 mg based on a range of trifluoroacetic acid composition of 1.0 to 2.2 equivalents.*

4 CONTRAINDICATIONS

Bivalirudin for Injection 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 Acute Stent Thrombosis in Patients with STEMI undergoing PCI

Acute stent thrombosis (AST) (<4 hours) has been observed at a greater frequency in Bivalirudin for Injection treated patients (1.2%, 36/2,889) compared to heparin treated patients (0.2%, 6/2,911) with STEMI undergoing primary PCI. Among patients who experienced an AST, one fatality (0.03%) occurred in a bivalirudin treated patient and one fatality (0.03%) in a heparin treated patient. These patients have been managed by Target Vessel Revascularization (TVR). Patients should remain for at least 24 hours in a facility capable of managing ischemic complications and should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischemia.

5.3 Coronary Artery Brachytherapy

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

If a decision is made to use Bivalirudin for Injection 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)]*.

5.4 Laboratory Test Interference

Bivalirudin affects International Normalized Ratio (INR), therefore INR measurements made in patients who have been treated with Bivalirudin for Injection may not be useful for determining the appropriate dose of warfarin.

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 6,010 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 (Safety Population)

	Bivalirudin with "provisional" GPI[1] (n=2,914)	**Heparin + GPI (n=2,987)**
Protocol defined major hemorrhage[2] (%)	2.3%	4.0%
Protocol defined minor hemorrhage[3] (%)		

	13.6%	25.8%
TIMI defined bleeding[4]		
- Major	0.6%	0.9%
- Minor	1.3%	2.9%
Non-access site bleeding		
- Retroperitoneal bleeding	0.2%	0.5%
- Intracranial bleeding	<0.1%	0.1%
Access site bleeding		
- Sheath site bleeding	0.9%	2.4%
Thrombocytopenia[5]		
<100,000	0.7%	1.7%
<50,000	0.3%	0.6%
Transfusions		
- RBC	1.3%	1.9%
- Platelets	0.3%	0.6%

[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 > 4g/dL, whether or not bleeding site is identified, spontaneous or non-spontaneous blood loss with a decrease in hemoglobin >3g/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 >5g/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 4,312 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)*

	Bivalirudin (n=2,161)	**Heparin (n=2,151)**
No. (%) Patients with Major hemorrhage[1]	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 transfusions	43 (2.0)	123 (5.7)

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

[1] 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 (>0.2%) Treatment-related Adverse Events (reactions)(through 30 days) in the REPLACE-2 Safety Population

	Bivalirudin with "provisional" GPI[1] (n = 2,914)	**Heparin + GPI (n = 2,987)**

	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)

[1] Note: A patient could have been more than one event in any category.

Abbreviation: AE = Adverse Event.

Table 5: Adverse Reactions Other Than Bleeding Occurring In ≥ 5% of Patients in Either Treatment Group in BAT Trial

	Treatment Groups	
Event	**Bivalirudin (n=2,161)**	**Heparin (n=2,151)**
	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 2,161 bivalirudin-treated patients and

2% of 2,151 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; pulmonary hemorrhage; cardiac tamponade; and INR increased.

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)]*.

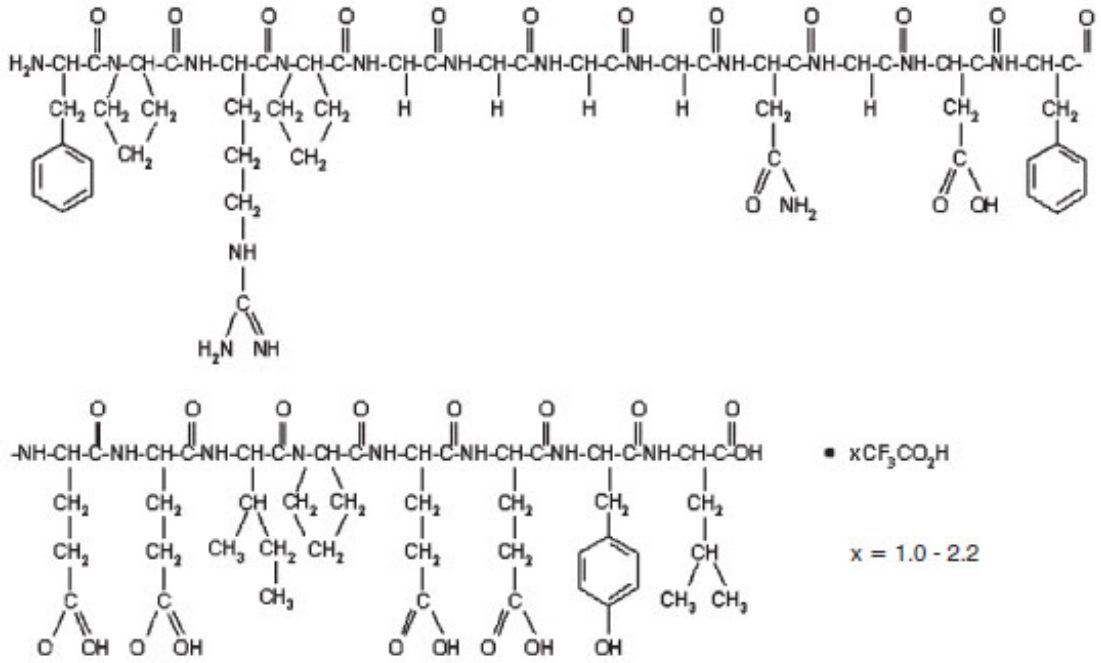
10 OVERDOSAGE

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 persons 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 overdosage, 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 for Injection contains bivalirudin which is a specific and reversible direct thrombin inhibitor. Bivalirudin is a synthetic, 20 amino acid peptide, with the chemical name of D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-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. The active pharmaceutical ingredient is in the form of bivalirudin trifluoroacetate as a white to off-white powder. The chemical name for bivalirudin trifluoroacetate is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-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 (Figure 1). The molecular weight of bivalirudin is 2,180 daltons (anhydrous free base peptide).

Figure 1. Structural formula for bivalirudin trifluoroacetate



Bivalirudin for Injection is supplied as a sterile white lyophilized cake, in single-dose vials. Each vial contains 250 mg bivalirudin, equivalent to an average of 270 mg of bivalirudin trifluoroactetate*, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5 to 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 to 6.

**The range of bivalirudin trifluoroacetate is 260 mg to 280 mg based on a range of trifluoroacetic acid composition of 1.0 to 2.2 equivalents.*

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 ≥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 ≥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 to 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 to 89 mL/min)	3.4	22
Moderate renal impairment (30 to 59 mL/min)	2.7	34
Severe renal impairment (10 to 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/m^2) 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 6,062 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 6,002 (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 10.9% of patients in the bivalirudin with provisional GPI arm. GPIs were administered to 7.2% of patients in the bivalirudin with provisional GPI arm (66.8% of eligible patients).

Patients ranged in age from 25 to 95 years (median, 63); weight ranged from 35 to 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%), positive ischemic stress test (24%), and other not specified indications (8%). 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 to 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 to 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% to 8.6%) in the bivalirudin with "provisional" GPI arm when compared to the heparin plus GPI arm (7.1%) (95% confidence interval 6.1% to 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=2,994)**	**Heparin + GPI (n=3,008)**
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[1,2]	2.4%	4.1%

[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.

[2] 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, 4,312 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 to 90 (median 63) years, their weight was a median of 80 kg (39 to 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 to 325 mg prior to PTCA and daily thereafter. Patients randomized to bivalirudin were started on an intravenous infusion of bivalirudin (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 (5^{th} percentile to 95^{th} percentile): 345 sec (240 to 595 sec) at 5 min and 346 sec (range 269 to 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=2,161)**	**Heparin (n=2,151)**
Efficacy Endpoints		
Procedural failure[1]	7.9%	9.3%
Death, MI, revascularization	6.2%	7.9%

Death	0.2%	0.2%
MI[2]	3.3%	4.2%
Revascularization[3]	4.2%	5.6%
Safety Endpoint		
Major hemorrhage[4]	3.5%	9.3%

[1] 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).

[2] Defined as: Q-wave MI; CK-MB elevation ≥2 x 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.

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

[4] Defined as the occurrence of any of the following: intracranial bleeding, retroperitoneal bleeding, clinically overt bleeding with a decrease in Hgb ≥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/mL (minimum 30% from prior to heparin), or has decreased to <150,000/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 to 89 years (median 70); weight ranged from 42 to 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-dose, glass vials. Each vial contains 250 mg of bivalirudin equivalent to an average of 270 mg of bivalirudin trifluoroacetate*.
**The range of bivalirudin trifluoroacetate is 260 to 280 mg based on a range of trifluoroacetic acid composition of 1.0 to 2.2 equivalents.*

Product No.	**NDC No.**	**Strength**	
PRX506210	63323-562-15	250 mg per vial	250 mg single-dose vial, packaged in tens.

Store Bivalirudin for Injection dosage units at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
The container closure is not made with natural rubber latex.

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.

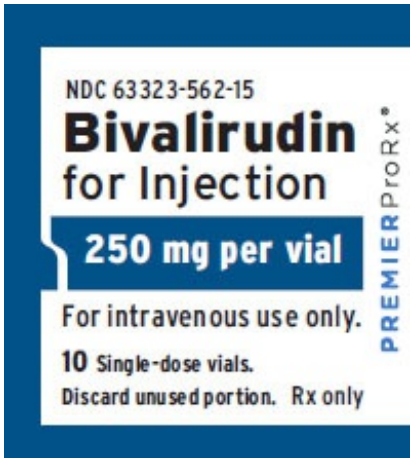
Advise patients to discuss with their health care provider their use of any other medications, including over-the-counter medications or herbal products, prior to bivalirudin use. Examples of other medications that should not be taken with bivalirudin are warfarin and heparin.

Manufactured by:
Fresenius Kabi
Lake Zurich, IL 60047
www.fresenius-kabi.com/us
451563
Revised: September 2017

PREMIERProRx®

PACKAGE LABEL - PRINCIPAL DISPLAY - Bivalirudin for Injection 250 mg Single Dose Vial Label
NDC 63323-562-41
Bivalirudin for Injection
250 mg per vial
For intravenous use only.
For single-dose only.
Discard unused portion.
Rx only

PACKAGE LABEL - PRINCIPAL DISPLAY - Bivalirudin for Injection 250 mg Single Dose Vial Tray Label
NDC 63323-562-15
Bivalirudin for Injection
250 mg per vial
For intravenous use only.
10 Single-dose vials.
Discard unused portion.
Rx only



BIVALIRUDIN

bivalirudin injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63323-562
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BIVALIRUDIN (UNII: TN9BEX005G) (BIVALIRUDIN - UNII:TN9BEX005G)	BIVALIRUDIN	250 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63323-562-15	10 in 1 CARTON	10/30/2017	
1	NDC:63323-562-41	1 in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090189	10/30/2017	

Labeler - Fresenius Kabi USA, LLC (608775388)

Establishment

Name	Address	ID/FEI	Business Operations
Fresenius Kabi USA, LLC		023648251	MANUFACTURE(63323-562)

Revised: 1/2020 Fresenius Kabi USA, LLC